

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y C

E. S. D.

REF: Expediente 06-110-229

TÍTULO SOLICITADO: "PREPARACIÓN FARMACÉUTICA PARA APLICAR SOBRE LA PIEL QUE CONTIENE DROSPIRENONA."

PUBLICACIÓN: Gaceta 579 de 31 de Agosto de 2007, número de publicación 300.

PRIORIDAD: DE 10 2004 016779-6 de 01/04/2004

SOLICITANTE: SCHERING AKTIENGESELLSCHAFT

APODERADO: J. IAN RAISBECK

TRÁMITE: SUSTENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LABORATORIO FRANCO-COLOMBIANO, LAFRANCOL S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2º de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada el 28 de Noviembre de 2007, en los siguientes términos:

I. RATIFICACIÓN

Comedidamente me permito exponer a continuación los argumentos que permitirán demostrar que la solicitud de la referencia, que reivindica una composición semisólida o líquida de drospirenona y etinil estradiol para ser

administrada por vía tópica a través de un dispositivo transdérmico, incumple los requisitos de patentabilidad establecidos por los artículos 14, 16 y 18 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario.

II. COMPLEMENTO DE INFORMACIÓN.

- La formulación transdérmica en forma de parche para la piel, es una forma de dosificación que se comercializa ampliamente desde aproximadamente 1979, fecha en la que la FDA aprueba dicha forma de dosificación para administrar escopolamina para el tratamiento de náuseas y mareo¹. Específicamente los parches transdérmicos tipo depósito (que pueden ser de tipo matricial o de reservorio) son formas de administración de liberación controlada ampliamente descritas y aplicadas en el estado de la técnica^{2,3,4}.

Si nos referimos específicamente a los parches transdérmicos utilizados como formas de administración de formulaciones contraceptivas también existen infinidad de publicaciones que demuestran la anterioridad en el uso de este tipo de dispositivos y para este tipo de terapia; como ejemplos de dichas aplicaciones se pueden mencionar la publicación internacional **WO/1994/005237** publicada el 17 de marzo de 1994 y titulada "PROTECTION AND UNDECEITFUL RIGID PATCH FOR CONTRACEPTIVE SHEATH; CONTRACEPTIVE SHEATH PROVIDED WITH SUCH PATCH"; la patente europea **EP 0754456** publicada el 22 de enero de 1997 y titulada "TOPICAL APPLICATION OF ST1435 AS A CONTRACEPTIVE AGENT"; la patente americana **US 5,798,347** publicada el 25 de agosto de 1998 y titulada "THERAPEUTIC METHODS AND DELIVERY SYSTEMS UTILIZING SEX STEROID PRECURSORS" ; la patente americana **US 6,071,531** publicada el 06 de junio de 2000 y titulada "TRANSDERMAL PATCH AND METHOD FOR ADMINISTERING

¹ FDA approves scopolamine patch to prevent peri-operative nausea. Food and Drug Administration (1997-11-10). Food and Drug Administration, U.S. Department of Health and Human Services. Public Health Service 5600 Fishers Lane Rockville, MD 20857. T97-59 Print Media: (301) 827-6242 November 10, 1997.

² J.L.Vila Jato, P. Bustamante Martínez, M.Guzman Navarro. Tecnología Farmacéutica. Volumen II, Parte 1, Capítulo 8, paginas 416 a 422. Ed.Sintesis S.A. Madrid España. 2001

³ La patente americana US 5352457 publicada el 04 de octubre de 1994 y titulada "TRASDERMAL DEVICE".

17-DEACETYL NORGESTIMATE ALONE OR IN COMBINATION WITH AN ESTROGEN" y la publicación internacional **WO/2000/076522** publicada el 21 de diciembre de 2000 y titulada "ADMINISTRATION OF NON-ORAL ANDROGENIC STEROIDS TO WOMEN"; todas estas, publicaciones que demuestran la gran utilidad y anterioridad en el uso de dichos dispositivos para este tipo de terapias contraceptivas.

De esta manera, queda demostrado que la inclusión de estos principios activos (andrógenos, estrógenos, anticonceptivos) dentro de este tipo de dispositivos transdérmicos no puede ser considerados como novedosos, o que tengan altura inventiva con respecto al arte anterior, además, es importante tener en cuenta que dicha inclusión puede obtenerse aplicando los respectivos ensayos de preformulación y formulación que todos los productos del mismo tipo deben seguir para poder obtener medicamentos eficaces, eficientes y seguros.

- Teniendo en cuenta lo anteriormente dicho, se ha demostrado hasta el momento que se cuenta con suficiente información para deducir una formulación en un dispositivo tipo parche transdérmico que contenga drospirenona y/o etinil estradiol con la finalidad de utilizarlo en terapia contraceptiva. A esto podemos sumarle el hecho que en el estado de la técnica también se encuentra ampliamente descrita la aplicabilidad de la combinación de estos dos principios activos en dicha terapia (etinil estradiol + drospirenona), como lo demuestran publicaciones como las siguientes, veamos:

- ❖ La patente americana US 5,583,129 publicada el 10 de diciembre de 1996 y titulada "COMPOSITION FOR CONTRACEPTION" revela:

⁴ La publicación internacional WO/1996/030000 publicada el 03 de octubre de 1996 y titulada "PHARMACEUTICAL COMPOSITION FOR TRANSDERMIC DELIVERY"

[57]

ABSTRACT

This invention relates to a method of inducing contraception comprising administering an estrogen selected from

2.0 to 6.0 mg of 17 β -estradiol and
0.015 to 0.020 mg of ethinylestradiol;
and a gestagen selected from

0.05 to 0.075 mg of gestodene,
0.075 to 0.125 mg of levonorgestrel,
0.06 to 0.15 mg of desogestrel,
0.06 to 0.15 mg of 3-ketodesogestrel,
0.1 to 0.3 mg of drospirenone,
0.1 to 0.2 mg of cyproterone acetate,
0.2 to 0.3 mg of norgestimate and
>0.35 to 0.75 mg of norethisterone

for a female of reproductive age, who has not yet reached premenopause, by administration for 23 or 24 days, beginning on day one of the menstrual cycle, followed by 5 or 4 pill-free or sugar pill days, during a total of 28 days in the administration cycle.

- ❖ La publicación internacional WO/95 17194 publicada el 29 de junio de 1995 y titulada "COMPOSITION FOR A CONTRACEPTIVE COMPRISING AN ESTROGEN AND A GESTAGEN" revela:

The invention concerns the use of a composition comprising an estrogen selected from 2.0-6.0 mg 17 β -estradiol and 0.015-0.020 mg ethinylestradiol and a gestagen selected from 0.05-0.075 mg gestodene, 0.075-0.125 mg levonorgestrel, 0.06-0.15 mg desogestrel, 0.06-0.15 mg 3-ketodesogestrel, 0.1-0.3 mg drospirenone, 0.1-0.2 mg cyproterone acetate, 0.2-0.3 mg norgestimate and >0.35-0.75 mg norethisterone, used to produce a dosage formulation for contraception for a woman of child-bearing age who has not reached premenopause by administering the dosage formulation during 23 or 24 days, beginning on day one of the menstrual cycle, followed by 5 or 4 pill-free or placebo days, over a complete 28-day cycle of administration, wherein the individual dosage formulations contain a constant amount of estrogen/gestagen throughout the 23 or 24 days. The invention also pertains to a combination oral contraceptive based on this composition.

- ❖ La publicación internacional WO 98/04269 publicada el 05 de febrero de 1998 y titulada "MONOPHASIC CONTRACEPTIVE METHOD AND KIT COMPRISING A COMBINATION OF A PROGESTIN AND ESTROGEN" revela:

This invention provides a method of contraception which comprises administering to a female of child bearing age for a combination of a progestin at a daily dosage of 40-500 μ g trimestone, 250 μ g - 4 mg dienogest, or 250 μ g - 4 mg drospirenone, and an estrogen at a daily dosage equivalent in estrogenic activity to 10-20 μ g ethinyl estradiol for 23-25 days beginning on day 1 of the menstrual cycle, and wherein the same dosage of the progestin and estrogen combination is administered in each of the 23-25 days.

- ♦ La patente americana US 5,858,405 publicada el 12 de enero de 1999 y titulada "ORAL CONTRACEPTIVE" revela:

1. A method of contraception which comprises administering orally to a female of child bearing age for 23-25 consecutive days,

a first phase combination of a progestin at a daily dosage selected from the group consisting of 40-500 μ g trimegestone, 250 μ g-4 mg dienogest, and 250 μ g-4 mg drospirenone, and an estrogen at a daily dosage equivalent in estrogenic activity to 10-20 μ g ethinyl estradiol for 3-8 days beginning on day 1 of the menstrual cycle, wherein the same dosage of the progestin and estrogen combination is administered in each of the 3-8 days,

- ♦ La publicación científica "DROSPIRENONE: PHARMACOLOGY AND PHARMACOKINETICS OF A UNIQUE PROGESTOGEN⁵" revela:

Abstract: The pharmacology and pharmacokinetics of drospirenone, a unique progestogen, are reviewed in this paper. Unlike other progestogens, drospirenone, an analogue of spironolactone, has biochemical and pharmacologic profiles similar to endogenous progesterone, especially regarding antimineralocorticoid and antiandrogenic activities. Drospirenone counteracts the estrogen-induced stimulation of the renin-angiotensin-aldosterone system and blocks testosterone from binding to androgen receptors. Because of these characteristics, it has the potential to reduce body weight, blood pressure, and low-density lipoprotein levels and to enhance high-density lipoprotein levels. As a combination oral contraceptive, drospirenone with ethinyl estradiol is effective and has positive effects on weight and lipid levels. Additionally, it relieves menstrually related symptoms (e.g., negative affect and water retention) that are commonly observed with other combination oral contraceptives. Based on the biochemical and pharmacodynamic data, drospirenone appears to be a viable alternative to the currently available progestogens.

Por ultimo, pero no menos importante, no solamente se encuentra información suficiente para derivar de manera obvia lo reivindicado en la solicitud colombiana en trámite, sino que además existen anterioridades que incluyen de manera idéntica estos dos principios activos, en formulaciones

⁵ Krattenmacher R. Drospirenone: pharmacology and pharmacokinetics of a unique progestogen. Contraception. 2000 Jul;62(1):29-38.

farmacéuticas para aplicación tópica y con los mismos componentes de la formulación, lo cual termina de desvirtuar contundentemente, junto con los argumentos anteriores, los requisitos tanto de novedad y de nivel inventivo de dicha solicitud en trámite, veamos:

- La publicación internacional WO 97/11680 publicada el 03 de abril de 1997 y titulada "HORMONE REPLACEMENT THERAPY METHOD AND HORMONE DISPENSER" revela:

Varying the daily dose of either or both of the estrogen and the progestogen administered for hormone replacement therapy (HRT) is readily and inexpensively accomplished, without the necessity of the physician prescribing a new product each time the daily dose of the estrogen or progestogen is changed, by administering preferably transdermally the estrogen and progestogen contained in separate extrudable pharmaceutical compositions from a dispenser which contains means, preferably adjustable only by the attending physician or dispensing pharmacist, for varying the volume of either or both of the respective compositions which is dispensed as a single dose from the dispenser in response to a defined digital dispensing manipulation of the dispenser, thereby facilitating optimal compliance to a combination HRT with individually adjusted dosages of the estrogen and progestogen.

(...)

c. the pharmaceutical compositions are adapted for transdermal administration, which preferably contain a transdermal absorption enhancing agent and they are adapted to be administered by rubbing into the skin or by applying the pharmaceutical compositions to a face of a skin patch which has an adhesive surface and then adhering the patch to the skin of the patient;

(...)

i. the delivery surface is a sheet and the hormone-containing compositions are transferred to the skin of the female by applying thereto the face of the sheet bearing the doses of the estrogen and the progestogen, which face optionally also comprises either or both of (i) indicia which identify the respective dosages of the estrogen and progestogen which are contained in the amount of extrudate applied to that face and (ii) an adhesive area surrounding the area to which the extrudate or extrudates are applied which is adapted for adhering the sheet to the skin of the female;

(...)

The Estrogen and Progestogen

The pharmaceutical compositions employed in the methods present in the article of manufactures of this invention comprise an estrogen and progestogen.

Examples of estrogens which can be employed in this invention (dosages shown are oral; transdermal dosages will vary therefrom in accordance with the

absorption efficacy of the vehicle employed) are ethinyl estradiol and mestranol (5 - 15 mcg/day), estradiol and their esters, e.g. valerate, acetate, benzoate and undecylate (0.5 - 4 mg/day), estriol, estriol succinate, polyestriol phosphate (2 - 8 mg), estrone, estrone sulfate and conjugated estrogens (0.3 - 1.2 mg/day). Of these, ethinyl estradiol, conjugated estrogens, estrone and especially 17 β -estradiol are preferred.

Examples of progestogens which can be employed in this invention (dosages shown are oral; transdermal dosages will vary therefrom in accordance with the adsorption efficacy of the vehicle employed) are micronized progesterone (100 - 200 mg/day), norethisterone and esters, e.g., acetate (0.5 - 2 mg/day), thereof, norgestrel (80 - 250 mcg/day), levo-norgestrel (40 - 125 mcg/day), chlormadinone acetate (1 - 2 mg/day), cyproterone acetate (1 - 2 mg/day), desogestrel, 3-ketodesogestrel (40 - 120 mcg/day), drospirenone (1 - 3 mg/day), norgestimate, or gestodene (20 - 80 mcg/day).

Of these, gestodene, levo-norgestrel, 3-ketodesogestrel, drospirenone and especially gestodene, levo-norgestrel and 3-ketodesogestrel are preferred.

(...)

The Pharmaceutical Compositions

The pharmaceutical compositions employed in the method of this invention and present in the dispensers of this invention contain the multiple doses of the estrogen or the gestagen in non-discreet form so that individual doses of any desired size can be dispensed therefrom, i.e., they are an extrudable viscous liquid, e.g., one which will flow after being transferred to the delivery surface, or

(...)

an extrudable semi-solid, e.g., a gel, ointment or creme which is dimensionally stable on the delivery surface, during the period between extrusion and application to the skin, or a spreadable solid, similar to a stick deodorant. When the composition is a viscous liquid, it preferably has a viscosity of 2,000-100,000 cps, more preferably 5,000-50,000 cps, so that it can be dispensed by a lotion-type pump dispenser and administered by spreading onto the skin by rubbing (topical administration). When the composition is a semisolid it preferably has a viscosity of 50,000-500,000 cps so that it can be extruded as a pasty mass and administered by either the oral or transdermal route. The compositions preferably have micropenetration values of less than $1000\text{mm} \times 10^{-1}$, preferably more than $1000\text{mm} \times 10^{-1}$. Measured by another method (extensometer test) the extensometer values are in the range of from 200mm^2 (more viscous) to 4000mm^2 (more fluid), preferably more than 4000mm^2 . As will be appreciated by those skilled in the art, there is no clear distinction between a very viscous extrudable liquid and a very soft extrudable semi-solid. For the purposes of this invention, they are both suitable.

(...)

The vehicle in which the estrogen or progestogen is dissolved or suspended can be aqueous, if the selected hormone therein is storage-stable, or nonaqueous, e.g., ethanol or methanol, and can contain one or more of the pharmaceutical carriers, adjuvants or excipients conventionally employed in a composition adapted for transdermal drug administration, and include any such materials known in the art, e.g., any liquid, gel, solvent, liquid diluent, solubilizer, or the like, which is nontoxic and which does not interact with other components of the composition in a deleterious manner. Examples of suitable adjuvants are water,

(...)

liquid glyceryl triesters with low molecular weight fatty acids or wax-like esters, lower alkanols, natural oils such as corn oil, groundnut oil, sesame oil, castor oil or condensation products thereof with ethylene oxide, and the like, hydrocarbons such as pharmaceutical grade mineral oil, silicones, emulsifiers such as monoglycerides or diglycerides of fatty acids, phospholipic acid derivatives such as lecithin or cephalin, polyalkylene glycols such as polyethylene glycol, aqueous phases to which a swelling agent such as sodium carboxymethylcellulose, sodium alginate, polyvinylpyrrolidone, etc., has been added and to which, in addition, dispersion agents or emulsifiers such as lecithin may be added, polyoxyethylene-derivatives and the like. The adjuvants may, in addition, contain additives such as preservatives, stabilizers, wetting agents, emulsifiers, etc. The composition preferably also contains a transdermal absorption enhancing agent, which can also serve as a carrier component. When the composition is a semi-solid, a conventional extrusion assist agent which reduces the energy required to extrude the composition preferably is present.

(...)

Topical Compositions

The pharmaceutical compositions employed in the method of this invention and in the dispensers of this invention are preferably administered by application to an appropriate area of the skin (or mucosa). Therefore, they preferably contain an effective amount of an absorption enhancing agent.

(...)

The Site of Administration

The site of administration will, of course, be determined by the nature of the pharmaceutical compositions containing the estrogen or the progestogen, which can be adapted for oral, transdermal or transmucosal administration. Transdermal administration is preferred.

(...)

Además reivindica:

3. A method according to claim 1, wherein the site of administration is an area of the skin of the female and the first and second pharmaceutically acceptable compositions are adapted to transdermal administration.

11. A method according to claim 1, wherein the estrogen is ethinyl estradiol or estradiol or an ester thereof, estrone, estrone sulfate or conjugated estrogens and the progestogen is micronized progesterone, norethindrone or esters thereof, norgestrel, chlormadinone acetate, cyproterone acetate, desogestrel, 3-ketodesogestrel, drospirenone, norgestimate, levo-norgestrel or gestodene.

12. A method according to claim 1, wherein the estrogen is ethinyl estradiol or 17 β -estradiol and the progestogen is gestodene, levonorgestrel or 3-ketodesogestrel.

Como se puede apreciar, en este documento se incluyen tanto la combinación de Drospirenona y Etinilestradiol, en formulaciones tópicas (parche transdérmico) líquidas y semisólidas, que pueden contener etanol y polivinilpirrolidona, así como un activador de la permeación; con lo cual queda desvirtuada la novedad de lo incluido en el capítulo reivindicatorio de la solicitud colombiana en trámite, específicamente en sus reivindicaciones 1, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14 y 15.

- Adicionalmente, la solicitud colombiana en trámite, en sus reivindicaciones 2, 3 y 11, menciona que la solubilidad saturada de la drospirenona es mejorada a través de la formulación que la contiene, explícitamente, en un factor que puede ir de 1.5 a 10; dichas características de solubilidad del principio activo no pueden ser tomadas como aporte novedoso al estado de la técnica, porque en realidad simplemente se trata de un reporte de las características de solubilidad de la drospirenona dentro de la formulación y que, como cualquier otra formulación del mismo tipo, pertenecen a características que se registran y se obtienen mediante la aplicación de los respectivos ensayos de preformulación y formulación, y mas específicamente, puede llegarse a un perfil de solubilidad deseado a través de estimaciones teóricas de solubilidad y de ensayos semiempíricos que combinan consideraciones tanto termodinámicas como parámetros experimentales. En el caso de la solicitud colombiana en trámite, en donde

se utilizan diversos solventes orgánicos, podría aplicarse, por ejemplo, el método Hildebrand⁶; así mismo, son reconocidos por cualquier persona medianamente versada en la materia, la existencia de diferentes métodos para mejorar la solubilización de fármacos⁷, entre los cuales se puede mencionar la co-disolución, método que se caracteriza por la combinación de diversos solventes que favorezcan la solubilidad del fármaco, tal y como sucede en el caso de la mezcla entre isopropanol, etanol y polivinilpirrolidona que se reivindica en la solicitud colombiana en trámite.

En conclusión, la solicitud colombiana en trámite busca reivindicar no solo la combinación farmacéutica de dos principios activos, en formulaciones farmacéuticas, ambos lo suficientemente descritos en el estado de la técnica, sino que además, lo contenido en sus respectivas reivindicaciones ya se encontraba descrito y aplicado para dar respuesta al mismo asunto en el mismo estado de la técnica, con lo que se hace evidente que la solicitud colombiana en trámite carece inobjetablemente de novedad y de nivel inventivo.

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales y que en consecuencia se decrete, además de la negación de la solicitud en comento, el archivo del expediente que la contiene.

III. ANEXOS

- Tecnología Farmacéutica. Volumen I, Parte 1, Capítulo 3, páginas 175 a 183 y 195 a 205.
- La publicación informativa de la FDA: "FDA TALK PAPER: FDA APPROVES SCOPOLAMINE PATCH TO PREVENT PERI-OPERATIVE NAUSEA".
- Tecnología Farmacéutica. Volumen II, Parte 1, Capítulo 8, páginas 416 a 422.

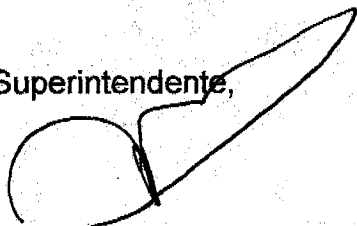
⁶ J.L.Vila Jato, P. Bustamante Martínez, M.Guzman Navarro. Tecnología Farmacéutica. Volumen I, Parte 1, Capítulo 3, páginas 175 a 183. Ed.Sintesis S.A. Madrid España. 2001.

⁷ J.L.Vila Jato, P. Bustamante Martínez, M.Guzman Navarro. Tecnología Farmacéutica. Volumen I, Parte 1, Capítulo 3, páginas 195 a 205. Ed.Sintesis S.A. Madrid España. 2001.

- La patente americana US 5,352,457 publicada el 04 de octubre de 1994 y titulada "TRASDERMAL DEVICE".
- Portada de la publicación internacional WO/1996/030000 publicada el 03 de octubre de 1996 y titulada "PHARMACEUTICAL COMPOSITION FOR TRANSDERMIC DELIVERY".
- Portadas de aplicaciones: Publicación internacional WO/1994/005237 publicada el 17 de marzo de 1994 y titulada "PROTECTION AND UNDECEITFUL RIGID PATCH FOR CONTRACEPTIVE SHEATH; CONTRACEPTIVE SHEATH PROVIDED WITH SUCH PATCH"; la patente europea EP0754456 publicada el 22 de enero de 1997 y titulada "TOPICAL APPLICATION OF ST1435 AS A CONTRACEPTIVE AGENT"; la patente americana US5,798,347 publicada el 25 de agosto de 1998 y titulada "THERAPEUTIC METHODS AND DELIVERY SYSTEMS UTILIZING SEX STEROID PRECURSORS" ; la patente americana US6,071,531 publicada el 06 de junio de 2000 y titulada "TRANSDERMAL PATCH AND METHOD FOR ADMINISTERING 17-DEACETYL NORGESTIMATE ALONE OR IN COMBINATION WITH AN ESTROGEN" y la publicación internacional WO/2000/076522 publicada el 21 de diciembre de 2000 y titulada "ADMINISTRATION OF NON-ORAL ANDROGENIC STEROIDS TO WOMEN".
- Portadas de: La patente americana US 5,583,129 publicada el 10 de diciembre de 1996 y titulada "COMPOSICIÓN FOR CONTRACEPCION"; la publicación internacional WO/95 17194 publicada el 29 de junio de 1995 y titulada "COMPOSICTION FOR A CONTRACEPTIVE COMPRISING AN ESTROGEN AND A GESTAGEN"; la publicación internacional WO 98/04269 publicada el 05 de febrero de 1998 y titulada "MONOPHASIC CONTRACEPTIVE METHOD AND KIT COMPRISING A COMBINATION OF A PROGESTIN AND ESTROGEN" y la patente americana US 5,858,405 publicada el 12 de enero de 1999 y titulada "ORAL CONTRACEPTIVE".
- Abstract de la publicación científica "DROSPIRENONE: PHARMACOLOGY AND PHARMACOKINETICS OF A UNIQUE PROGESTOGEN".
- La publicación internacional WO 97/11680 publicada el 03 de abril de 1997 y titulada "HORMONE REPLACEMENT THERAPY METHOD AND

HORMONE DISPENSER" paginas 11, 15, 14, 16, 17, 19 y capítulo reivindicatorio.

Señor Superintendente,



JOSE LUIS REYES VILLAMIZAR
C.C. 79.152.473 de Usaquén
T.P. 44655 del C. S de la J.

FDA TALK PAPER

Food and Drug Administration

U.S. Department of Health and Human Services

Public Health Service 5600 Fishers Lane Rockville, MD 20857

FDA Talk Papers are prepared by the Press Office to guide FDA personnel in responding with consistency and accuracy to questions from the public on subjects of current interest. Talk Papers are subject to change as more information becomes available.

T97-59

November 10, 1997

Print Media: (301) 827-6242

Consumer Hotline: (800) 532-4440

FDA APPROVES SCOPOLAMINE PATCH TO PREVENT PERI-OPERATIVE NAUSEA

FDA is receiving inquiries about the October 27 approval of Novartis Consumer Health's scopolamine patch (Transderm Scop) for prevention of perioperative nausea. The following can be used to answer questions:

The scopolamine patch was initially approved as a prescription drug in December 1979 to prevent the nausea and vomiting associated with motion sickness. However, in 1994, the manufacturer removed the product from the marketplace due to manufacturing problems. Only very recently has the patch returned to the marketplace.

The recent approval, however, is for an additional indication: preventing the nausea and vomiting related to some anesthesia and certain pain relievers used during or after surgery. The patch is for single use only and should not be worn for more than three days. It also should not be used by children.

The tan-colored scopolamine patch is small and placed behind the ear the night before surgery or an hour before cesarean section.

The most common side effect experienced by people who use the scopolamine patch is dryness of the mouth, which occurs in about two-thirds of those people. Drowsiness, temporary blurring of vision and widening of the pupils may also occur.

Novartis Consumer Health is located in Summit, N.J.

###

FDA HOME PAGE



US005352457A

United States Patent [19]

Jenkins

[11] Patent Number: 5,352,457

[45] Date of Patent: Oct. 4, 1994

[54] TRANSDERMAL DEVICE

[75] Inventor: Anthony W. Jenkins, Comberton,
United Kingdom[73] Assignee: Ethical Pharmaceuticals Limited,
Ely, United Kingdom

[21] Appl. No.: 30,265

[22] PCT Filed: Oct. 4, 1991

[86] PCT No.: PCT/GB91/01730

§ 371 Date: Apr. 5, 1993

§ 102(e) Date: Apr. 5, 1993

[87] PCT Pub. No.: WO92/03811

PCT Pub. Date: Apr. 16, 1992

[30] Foreign Application Priority Data

Oct. 5, 1990 [GB] United Kingdom 9021674.8

[51] Int. Cl.⁵ A61F 13/02

[52] U.S. Cl. 424/448; 424/449

[58] Field of Search 424/448, 449

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Patent Abstracts of Japan, vol. 12, No. 333 (C-526),
Sep. 8, 1988.Patent Abstracts of Japan, vol. 12, No. 159, (C-495),
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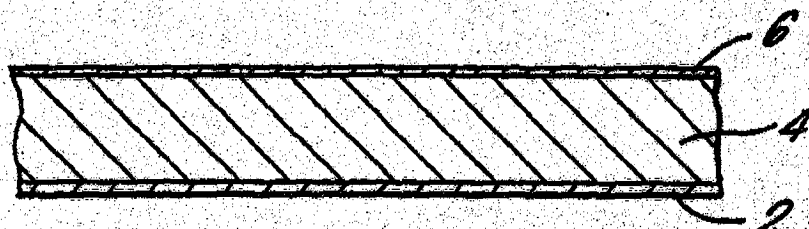
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[57] ABSTRACT

The invention pertains to a method of preparing a device for transdermal delivery of an active ingredient which is solid at room temperature and in which part or all of the active ingredient is present in a saturated or supersaturated solution. In the first step, a mixture is prepared which includes at least a polymer adhesive, a vehicle for the polymer adhesive, an active ingredient and a solvent mixture for the active ingredient which solvent mixture comprises at least two solvents having different boiling points. The mixture is then formed into a film and dried. The vehicle for the polymer adhesive and at least one of the solvents and the solvent mixture have boiling points below the drying temperature of the film, while at least one of the solvents in the solvent mixture has a boiling point above the drying temperature of the film. Thus, at least one of the solvents remains in the film after drying and the solubility of the active ingredient contained in the remaining solvent is greater than 10%.

29 Claims, 3 Drawing Sheets



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FIG. 1.

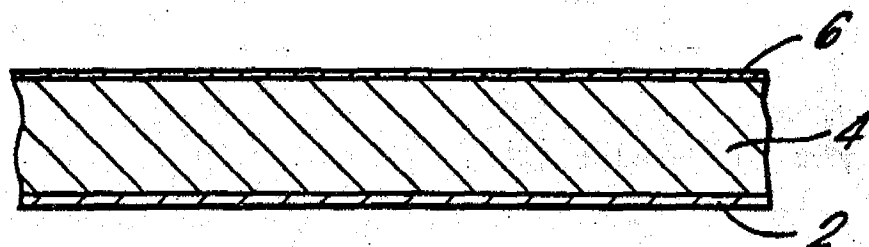
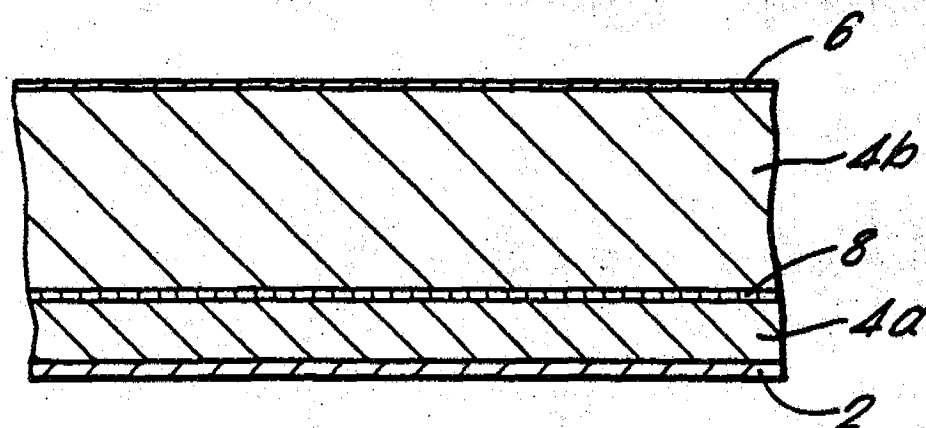
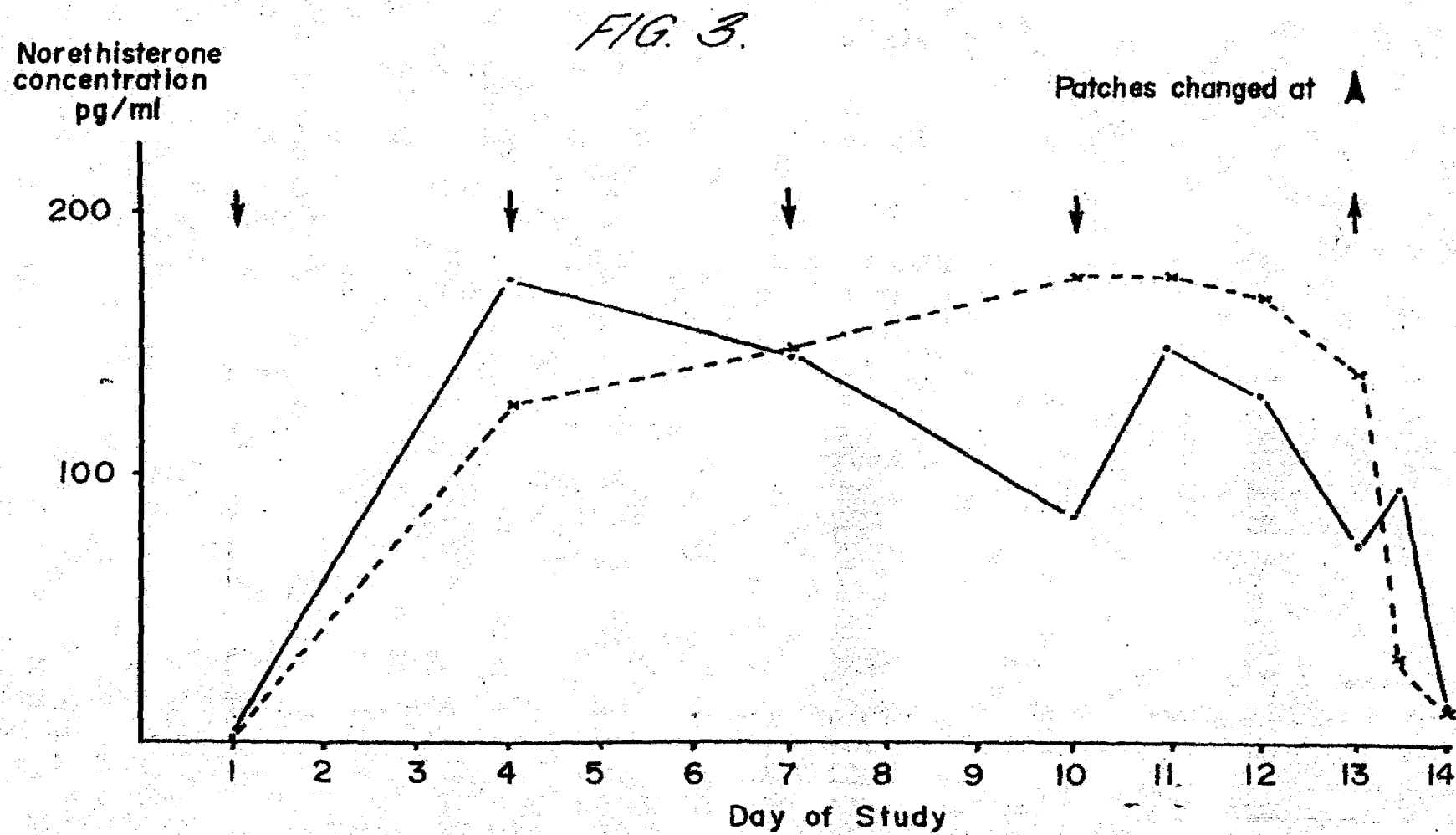


FIG. 2.





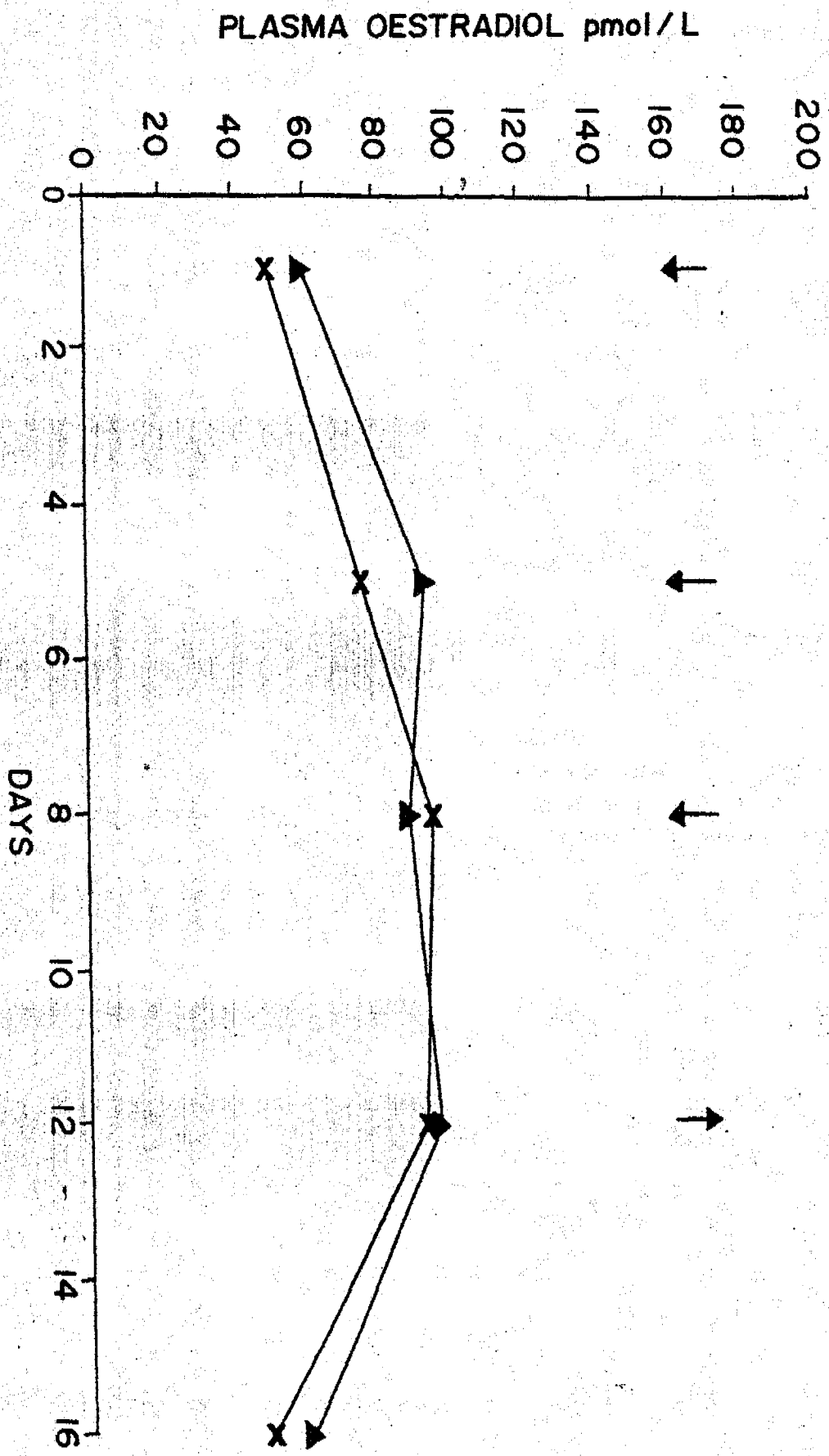


FIG. 4

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TRANSDERMAL DEVICE

The invention relates to a method of preparing a device for transdermal delivery of an active ingredient and to transdermal devices prepared by that method.

The administration of drugs through the skin is a concept which is now well established and this route has several advantages over more conventional forms of drug delivery such as injection or oral ingestion. A particular advantage is that transdermal drug delivery devices can provide a sustained and controlled release of the active ingredient over a prolonged period so that the resulting blood levels remain constant. This is in contrast to other forms of administration where surges of the agent occur in the bloodstream immediately after administration and then drop away rapidly until the next dose is given. In the case of oral administration the blood level is further influenced by contents of the intestines and therefore difficult to control. Transdermal administration permits direct access to the bloodstream without first passage through the gastrointestinal tract and liver and also without the inherent problems associated with injection such as risk of infection and need for sterile administration equipment.

Because of the advantage of transdermal administration, in recent years a very large number of devices have been developed and described for the transdermal administration of a variety of pharmaceuticals. The devices are usually in the form of a patch or plaster to be attached to the skin. Early devices such as for example, that described in U.S. Pat. No. 3,598,122 comprised a reservoir containing the active ingredient, either in solid or liquid form. The reservoir walls were composed of a material permeable to that ingredient and it was stuck to the skin by a thin layer of adhesive which was also permeable to the active ingredient. The outer surface of the reservoir was covered with a backing material impermeable to the active ingredient. Such devices were bulky and solvents in which the active agent was dissolved tended to interfere with the ability of the adhesive to stick to the skin.

With improvements in adhesives available it was soon found possible, and indeed preferable, to prepare transdermal devices in which the adhesive layer itself provided the drug reservoir. Thus more modern transdermal devices usually comprise at least an impermeable backing material, a layer of drug-containing adhesive attached to the backing material and a release liner on the other adhesive surface which is removed for application of the device to the skin. Additional membranes are sometimes included within the device to regulate the rate of passage of the active agent from the adhesive to the skin.

Various methods have been used to achieve suitable drug/adhesive mixtures in which the active ingredient is dispersed in the adhesive without affecting the ability of the adhesive to stick to the skin. One of the earliest drugs to be administered by a transdermal device was nitroglycerin which is used in the treatment of angina pectoris and congestive cardiac failure. Nitroglycerin is well absorbed by the skin and therefore particularly amenable to transdermal administration. Conveniently it is a liquid at room temperature and so the approach that has been taken is to absorb it on to a solid such as lactose which is then dispersed in a polymer adhesive. Such devices are described in, for example U.S. Pat. No. 4,776,850, G.B. 2,081,582, and others. One or more

other "solvents" are sometimes present in the nitroglycerin adhesive mixtures either as permeation enhancers, or for the purpose of "solvent casting" the mixture onto a backing layer.

Where the active ingredient to be incorporated into a transdermal device is a solid any solvent for the agent must be carefully chosen to be compatible with the adhesive. In WO86/00814 for example the problem is overcome by choosing a single solvent which is both a solvent for the drug and a solvent for the adhesive. However such a method restricts severely the number of different drugs which are compatible with a particular adhesive and also the type of adhesive which can be used.

Alternative methods have therefore been used in which a drug/adhesive mixture is prepared, which includes a solvent for the drug and a solvent for the adhesive. The mixture is spread onto an appropriate backing material and then dried to evaporate the solvents leaving the drug dispersed in the adhesive in particulate form. A variation of the method is described in WO89/07951 in which the solvents for the adhesive are evaporated during a drying stage leaving the drug, in this case oestrogen, dispersed in particulate form in very high boiling point solvents which do not significantly evaporate on drying but which have a low capacity for the drug.

While the active ingredient can be taken up by the skin from a dispersion of the solid compound, the rate of uptake can be far better controlled if the agent is in a supersaturated solution, particularly where the solvent has an adequate capacity for the active ingredient. As the ingredient is taken up by the skin more will become dissolved in solution so maintaining a concentration gradient over a prolonged period which drives uptake through the skin. Transdermal devices are known which contain saturated drug solutions. They are described for example in G.B. 2,156,215 and U.S. Pat. No. 4,201,211. However these documents fail to describe a way in which the level of saturation can be precisely controlled to produce a supersaturated solution.

The present invention provides an improved method for preparing transdermal devices which contain supersaturated solutions of an active ingredient within an adhesive layer by use of a carefully selected mixture of solvents and selective evaporation of a particular solvent or solvents by drying at a temperature above the boiling points thereof, to influence the final concentration of the solution of active ingredient in the device.

In accordance with the invention a method of preparing a device for transdermal delivery of an active ingredient which is a solid at room temperature and in which part or all of the active ingredient is present in a supersaturated solution comprises the steps of:

- (a) preparing a mixture comprising at least
 - (i) a polymer adhesive
 - (ii) a vehicle for the polymer adhesive
 - (iii) the active ingredient
 - (iv) a solvent mixture for the active ingredient which comprises at least two solvents;
- (b) forming the mixture prepared in step (a) into a film, and
- (c) drying the film prepared in step (b) wherein the vehicle for the polymer adhesive and at least one of the solvents in the solvent mixture for the active ingredient have boiling points below the drying temperature and at least one of the solvents in the solvent mixture for the active ingredient has a boil-

ing point above the drying temperature and wherein the solubility of the active ingredient in the said solvent or solvents having a boiling point above the drying temperature is greater than 10%.

The above method provides a very precise way of preparing an adhesive/active ingredient mixture which contains a supersaturated solution of the ingredient after drying.

It is to be understood herein that the term "active ingredient" is intended to mean a single active agent or a combination of more than one active agent.

Dissolving the active ingredient in a mixture of solvents and then drying at a temperature which facilitates the evaporation of the vehicle for the adhesive and one of the solvents for the active ingredient, because it is above their boiling points, leaves the active ingredient in a supersaturated solution in the solvent or solvents that remain. Supersaturated solutions are particularly advantageous from the point of view of transdermal administration because they assist in controlling the rate of migration of the active ingredient through the skin as previously mentioned.

The choice of particular solvents, adhesives and drying temperatures is dictated by the solubility of the particular active ingredient in the solvent or solvents remaining in the device after drying. Thus with careful selection of all the components the method of the invention can provide transdermal devices which can administer a very wide range of drugs. The solubility of the active ingredient in the solvent or solvents having a boiling point above the drying temperature needs to be greater than 10%.

The polymer adhesive may be a polyisobutylene or silicone adhesive although acrylate polymer adhesives are particularly preferred. Suitable vehicles for the acrylate adhesives are for example methanol, ethanol, industrial methylated spirits (IMS), isopropanol and water. Suitable vehicles which may be used with polyisobutylene are toluene, xylene and methylene chloride. Suitable vehicles for silicone adhesives are chlorofluorocarbons such as, for example, trichlorotrifluoroethane. For acrylate adhesives aqueous dispersions are preferred. In this latter case drying temperatures used in drying the film must always be in excess of 100° C. at normal atmospheric pressures. Where the vehicle for the adhesive is a lower boiling solvent such as methanol (bp 65° C.), ethanol (bp 78.5° C.) or isopropanol (bp 82.4° C.), a lower drying temperature may be used providing it is above the boiling point of the low boiling solvent included in the solvent mixture for the active ingredient.

In one embodiment of the invention the vehicle for the adhesive and the solvent to be evaporated during drying from the solvent mixture for the active ingredient both are chosen to have a boiling point below that of ethanol. A drying temperature can thus be chosen which allows the ethanol to be maintained within the device. This is advantageous because ethanol is a useful skin permeation enhancer for some drugs. For acrylate systems a suitable solvent which may be evaporated while ethanol is retained is methanol. For non-aqueous systems ether or chlorofluorocarbons may be used.

In another embodiment of the invention the solvent in the solvent mixture for the active ingredient which is evaporated on drying may be ethanol, isopropanol, industrial methylated spirits (IMS) or water.

High boiling point solvents suitable for forming the saturated or supersaturated solutions of the active ingre-

dient in the transdermal device are those having boiling points in excess of 110° C. Preferred solvent mixtures include one or more of diethylene glycol, propylene glycol, propylene carbonate, glycerol, lower molecular weight polyethylene glycols, propylene glycol esters, polyol fatty acid esters, fatty alcohol derivatives, oleic acid, iso-octyl stearate, iso-propyl myristate, isopropyl palmitate, ethyl oleate, diisopropyl adipate, diethylsuccinate, hexylaurate, triglycerides of caprylic or capric acids, diethyltoluamide, laurocapram, n-methylpyrrolidone and diethylene glycol monoether. Also suitable as solvents which are not evaporated from the device on drying are essential oils such as eucalyptus oil, tea-tree oil and lavender oil. Preferably at least one of the solvents which remains in the device will also act as a permeation enhancer to assist uptake by the skin of the active ingredient. Preferred solvent systems are propylene glycol-diethyltoluamide, n-methylpyrrolidone-diethyltoluamide, propylene glycol - diethylene glycol monoethyl ether and diethyltoluamide-diethylene glycol monoethyl ether - tea tree oil.

Among the active agents which may be included in transdermal devices produced by the method of the invention are anti-histamines such as, for example, clemastine fumarate, steroid hormones such as oestradiol, progestins such as norethisterone acetate, norgestrel, ethynodiol diacetate, medroxy progesterone acetate, gestodene and desogestrel, vasodilators such as nifedipine and diltiazem, antihypertensives such as clonidine and propranolol, bronchodilators such as salbutamol and clenbuterol, anti-tumour agents such as methotrexate and 5-fluorouracil, alkaloids such as physostigmine and analgesics such as fentanyl, sufentanil, buprenorphine and hydromorphone. The device may contain an active ingredient which is a combination of more than one of the above active agents, for example an oestrogen with a progestin.

While the solvents to be used in the method of the invention must be selected in order that a supersaturated solution is produced on drying, solvents may also be selected which modify the properties of the adhesive so that it possesses the required degree of adhesion and tackiness to stick to the skin for the required period, which could be several days, but at the same time can be easily removed as required. The method of the present invention allows polymer adhesives which are normally too aggressive to be used in transdermal devices to be rendered suitable by choice and incorporation of an appropriate solvent mixture.

The assembly of a transdermal device prepared in accordance with the method of the present invention will now be described by way of example with reference to FIGS. 1 and 2 of the accompanying drawings and Examples 1 to 4.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a vertical section through a first embodiment of the invention without the inclusion of a rate control membrane.

FIG. 2 is a vertical section through a second embodiment of the invention including a rate control membrane.

FIG. 3 shows mean plasma concentration time curves following transdermal administration of norethisterone acetate to four post menopausal women using a transdermal device prepared in accordance with the method of the invention — results from samples assayed by RIA at Liverpool University. x—x results from same

samples assayed by RIA at Hammersmith Hospital. ↑ transdermal patches applied or replaced. ↓ transdermal patches removed.

FIG. 4 shows mean plasma concentration time curves following transdermal administration of oestradiol using the devices of Example 4 (▲—▲) and known product Estraderm 50 (X—X). The arrows indicate patches applied, replaced or removed as above.

As already described, a mixture is formed which comprises a polymer adhesive in a suitable vehicle, the active ingredient to be administered, and a solvent mixture for the active ingredient which comprises at least two solvents one of which must have a boiling point above the drying temperature and one below. Preferably the active ingredient is first dissolved in the solvent mixture and the solution slowly added to the adhesive polymer previously dispersed in a suitable vehicle. Depending on the coating technique and adhesive used the addition of an adhesive thickener may be required. The mixture of adhesive polymer and active ingredient is formed into a film, preferably by coating onto a flexible sheet material. A typical embodiment of a device formed in accordance with the method of the invention is shown in FIG. 1. The adhesive mixture is formed into a layer 4 on a siliconised release paper 2. The layer is preferably about 5 to 500 μm thick. The coated release paper is dried at the appropriate temperature to drive off the necessary solvents and then laminated to a backing material 6 impermeable to the active ingredient. Suitable siliconised release liners are 3M Health Care Type 660 or 1360, Daubert HDPE 164Z or L. Stace types 635/6. Preferable backing materials include polyester film laminate (e.g. 3M Health Care Type 1012 or 1220), metalised polyester laminate (e.g. 3M Health Care Type 1109) and co-extruded high barrier films either clear (e.g. BXL Plastics Hybar) or skin-tone (e.g. Grace-Cryovac MF200). Backings having higher oxygen and water vapour transmission rates are preferred for devices intended for treatment for more than 24 hours. A suitable backing material in these circumstances is Semex polyester-urethane film type MF 4387-00.

The reverse manufacturing method is also possible and in some cases advantageous i.e. spreading the adhesive/solvent mixture onto the backing material and then laminating it to the release liner.

FIG. 2 shows a second embodiment of the invention in which the adhesive/active ingredient layer is divided by a rate control membrane 8. The layer 4a which, in use, is in direct contact with the skin provides an initial loading dose of the active ingredient. As this migrates into the skin the consequent concentration difference between layer 4a and 4b causes the layer 4a to be replenished with active ingredient from the layer 4b at a rate dictated by the rate control membrane. Thus the inclusion of such a membrane provides a further means to control the rate of uptake for a pre-determined period, firstly by selection of the appropriate membrane and secondly by varying the thickness of the layers 4a and 4b on either side of the membrane. Suitable materials for forming the rate control membrane include polypropylene film (e.g. Celgard microporous film), polyvinyl acetate film (e.g. Mowiol film (Hoechst) and ethyl vinyl acetate film (e.g. controlled caliper MSP series films obtained from 3M Health Care Speciality Division). The thickness of the layer 4a may be in the range 5 to 50 μm and the thickness of the layer 4b may be in the range 50 to 500 μm .

The device of FIG. 2 is formed as previously described except that when using conventional coating/drying equipment the process becomes two stages. The backing material 6, coated with adhesive layer 4b is laminated to rate control membrane 8. The second stage is the lamination of this laminate to the adhesive layer 4a which has been coated on to the release paper 2. Alternative manufacturing methods are possible and more than one rate control membrane can be incorporated at any location within a multilayer device. Preferably all of the above described layers are assembled on a single large sheet which is die cut into transdermal devices of the appropriate size.

EXAMPLE 1

Transdermal Device Containing Norethisterone Acetate Without A Rate Control Membrane

A mixture of acrylate polymer adhesive and the active ingredient norethisterone acetate is formed containing the following:

Component	Quantity (g)
Norethisterone acetate (micronised)	395
Propylene glycol	2125
Diethyltoluamide	1000
Ethanol (95%) or IMS	1500
Primal N560 (acrylate adhesive dispersion in water)	44500
Acrysol ASE 60 (thickener for adhesive diluted 50:50)	480
Total	50 Kg

The norethisterone acetate is dissolved in propylene glycol, diethyltoluamide and ethanol by sonication or warming. This solution is added slowly to the aqueous acrylate adhesive dispersion (Primal N560, Rohm & Hass) with mixing. An adhesive thickener (Acrysol ASE 60) is then added to the mixture as a 50% solution/water mix sufficient to produce a thicker spreading solution of around 800 cP (Brookfield) for reverse roll coating or 60,000 cP to suit knife over roll coating.

The mixture is coated on the backing polyester (3M Health Care Type 1109) at about 100 μm wet coating thickness and dried at about 105° C. to drive off the water and the ethanol or IMS from the acrylate adhesive. The resulting dried adhesive layer is about 55 μm thick. The release liner (Stace type 636) is laminated to the adhesive layer. The final sheet is die-cut to form transdermal devices of about 19 or 28.5 cm^2 each containing 1.5 or 2.25 mg norethisterone acetate respectively, which are packaged individually.

EXAMPLE 2

Transdermal Device Containing Oestradiol With Rate Control Membrane

A mixture is prepared containing the following:

Component	Quantity (g)
17 β Oestradiol	87.5
Propylene glycol	400
Diethyltoluamide	100
95% Ethanol or IMS	100
Polysorbate 20	12.5
Primal N560 (acrylate adhesive dispersion)	4262.5
Acrysol ASE 60 (thickener for adhesive) 50:50 water	37.5

-continued

Component	Quantity (g)	
	Total	5000 g

The oestradiol is dissolved in the solvent mixture and slowly added to the aqueous adhesive to which an Acrysol ASE 60 thickener is also added in a similar way to Example 1. The mixture is coated onto a siliconised release liner (3M Health Care Type 660) to give a 50 μ m wet coating which is dried at 105° C. as described above. When dried the adhesive layer and liner are laminated to a rate control membrane sheet material (3M ethyl vinyl acetate membrane, MSP 987192) which is then coated with a 250 μ m wet coating of the same adhesive mixture and dried as before. The adhesive layers are then laminated to the clear polyester film laminate backing material as described. The sheets are cut into 20 cm² transdermal devices each containing 10.5 mg oestradiol and individually packaged for use.

EXAMPLE 3**Transdermal Device Containing Oestradiol Without A Rate Control Membrane**

A mixture is prepared containing the following:

Component	Quantity (g)
17 β oestradiol	440
Diethyltoluamide	2250
Isopropanol	60
Primal N560	47000
Acrysol ASE 60:water (50:50)	250
Total	50 Kg

The devices are prepared and assembled as described in Example 1. The release liner is coated to a wet-coat thickness of 100 μ m and after drying and laminating the laminate is die cut to 28.5 cm² devices each containing 2.5 mg oestradiol.

EXAMPLE 4**Transdermal Device Containing Oestradiol Without A Rate Control Membrane**

A mixture is prepared containing the following:

Component	Quantity (g)
17- β Oestradiol (micronised)	30
Diethyltoluamide	100
Diocylsodium sulphosuccinate	3
Isopropanol/water 50:50	2
Primal N560	655
Primal N582	200
Acrysol ASE 60:water 50:50	q.s. 10
Total	1000 g

The devices are prepared and assembled as described in Example 1 except that the devices are cut to 20 cm². Results obtained in a 4 subject pharmacokinetic study in comparison with an existing product (Estraderm 50) are shown in FIG. 4.

EXAMPLE 5**Transdermal Device Containing Buprenorphine Without A Rate Control Membrane**

A mixture is prepared containing the following:

Component	Quantity (g)
Buprenorphine	42
Ethanol or IMS	100
Diethyltoluamide	150
Diethylene Glycol Monoethyl ether	150
Tea Tree oil	100
Primal N560	3908
Primal N582	500
Acrysol ASE 60:water 50:50	50
Total	5000 g

The devices are prepared and assembled as described in Example 1 except that the release liner is coated to a wet coat thickness of 150 μ m and after drying the laminate is cut to 20 and 50 cm² devices containing 2.5 mg/20 cm² or 6.3 mg/50 cm² buprenorphine respectively.

It is to be noted that the terms Hybar, Cryovac, Celgard, Mowiol, Contran, Primal, Acrysol, Brookfield, Triton and Estraderm, used in the specification are Registered Trade Marks.

I claim:

1. A method of preparing a device for transdermal delivery of an active ingredient which is a solid at room temperature and in which part or all of the active ingredient is present in a supersaturated solution comprising the steps of:

(a) preparing a mixture comprising at least:

(i) a polymer adhesive which is selected from the group consisting of acrylate polymer adhesives, polyisobutylene adhesives, and silicone adhesives;

(ii) a vehicle for the polymer adhesive, which vehicle is selected from the group consisting of water, ethanol, industrial methylated spirits, isopropanol, toluene, xylene, methylene chloride, and chlorofluorocarbon;

(iii) the active ingredient;

(iv) a solvent mixture for the active ingredient which comprises at least two solvents having different boiling points;

(b) forming the mixture prepared in step (a) into a film, and

(c) drying the film prepared in step (b), wherein the vehicle for the polymer adhesive and at least one of the solvents in the solvent mixture for the active ingredient have boiling points below the drying temperature, and at least one of the solvents in the solvent mixture for the active ingredient has a boiling point above the drying temperature, and wherein the solubility of the active ingredient in the said solvent or solvents having a boiling point above the drying temperature is greater than 10%.

2. A method as claimed in claim 1 wherein the vehicle for the polymer adhesive is a solvent having a boiling point below that of ethanol.

3. A method as claimed in claim 2 wherein the vehicle for the polymer adhesive is methanol.

4. A method as claimed in claim 1 wherein the vehicle for the polymer adhesive is water.

5. A method as claimed in claim 1 wherein the solvent in the solvent mixture for the active ingredient with a boiling point below the drying temperature is selected from the group consisting of ethanol, industrial methylated spirits, isopropanol and water.

6. A method as claimed in claim 2 wherein the solvent in the solvent mixture for the active ingredient with a

boiling point below the drying temperature is a solvent having a boiling point below that of ethanol.

7. A method as claimed in claim 6 wherein the solvent in the solvent mixture for the active ingredient with a boiling point below the drying temperature is methanol.

8. A method as claimed in claim 1 wherein the solvent mixture for the active ingredient comprises at least one solvent having a boiling point above the drying temperature selected from the group consisting of diethylene glycol, propylene glycol, propylene carbonate, glycerol, lower molecular weight polyethylene glycols, propylene glycol esters, polyol fatty acid esters, fatty alcohol derivatives, oleic acid, iso-octyl stearate, isopropyl myristate, isopropyl palmitate, ethyl oleate, diisopropyl adipate, diethylsuccinate, hexylaurate, triglycerides of caprylic or capric acids, diethyl toluamide, laurocapram, n-methylpyrrolidone, diethylene glycol monoethyl ether and essential oils.

9. A method as claimed in claim 1 wherein the drying step (c) is carried out at or above 100° C.

10. A method as claimed in claim 1 wherein the drying step (c) is carried out at a temperature below the boiling point of ethanol.

11. A method as claimed in claim 1 wherein the active ingredient comprises at least one active agent selected from the categories antihistamines, steroid hormones, progestins, vasodilators, antihypertensives, bronchodilators, anti-tumor agents, alkaloids and analgesics.

12. A method as claimed in claim 1 wherein the film prepared in step (b) is formed by coating the mixture prepared in step (a) onto a thin flexible sheet material.

13. A method as claimed in claim 12 wherein the thin flexible sheet material is a siliconised release liner.

14. A method as claimed in claim 12 wherein the flexible sheet material is a backing material impermeable to the active ingredient.

15. A method as claimed in claim 12 wherein the film formed in step (b) is between 5 μ m and 500 μ m thick.

16. A method as claimed in claim 13 wherein the coated surface of the release liner is laminated to a backing material impermeable to the active ingredient.

17. A method as claimed in claim 14 wherein the coated surface of the impermeable backing material is laminated to a siliconised release liner.

18. A method as claimed in claim 13 wherein the coated surface of the release liner is laminated to a rate control membrane the free surface of which is further coated with the mixture prepared in step (a).

19. A method as claimed in claim 14 wherein the coated surface of the backing material is laminated to a rate control membrane, the free surface of which is further coated with the mixture prepared in step (a).

20. A method as claimed in claim 18 wherein the coated rate control membrane is laminated to a further rate control membrane or to a backing material impermeable to the active ingredient.

21. A method as claimed in claim 18 wherein the coated rate control membrane is laminated to a further rate control membrane or to a siliconised release liner.

22. A method as claimed in claim 18 wherein the thickness of the adhesive/active ingredient layer on either side of the rate control membrane is varied to control the rate of migration across the membrane.

23. A method as claimed in claim 19 wherein the thickness of the adhesive/active ingredient layer on either side of the rate control membrane is varied to control the rate of migration across the membrane.

24. A method as claimed in claim 18 wherein the thickness of the adhesive/active ingredient layer on either side of the rate control membrane is varied to control the proportion or amount of active ingredient immediately available adjacent to the skin for absorption.

25. A method as claimed in claim 19 wherein the thickness of the adhesive/active ingredient layer on either side of the rate control membrane is varied to control the proportion or amount of active ingredient immediately available adjacent to the skin for absorption.

26. A method as claimed in claim 14 wherein the backing material impermeable to the active ingredient is selected from the group consisting of a polyester film laminate, metalised polyester laminate co-extruded high barrier film and an air and water permeable polyurethane.

27. A method as claimed in claim 18 wherein the rate control membrane is selected from the group consisting of polypropylene film, a polyvinyl acetate film and an ethylvinyl acetate film.

28. A method as claimed in claim 19 wherein the rate control membrane is selected from the group consisting of polypropylene film, polyvinyl acetate film and ethylvinyl acetate film.

29. A device for transdermal delivery of an active ingredient prepared by the method as claimed in claim 1.

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DEMANDE INTERNATIONALE PUBLIÉE EN VERTU DU TRAITE DE COOPERATION EN MATIERE DE BREVETS (PCT)

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(54) Title: PHARMACEUTICAL COMPOSITION FOR TRANSDERMIC DELIVERY (54) Titre: COMPOSITION PHARMACEUTIQUE FILMOGENE POUR ADMINISTRATION TRANSDERMIQUE (57) Abstract A pharmaceutical composition for transdermal delivery including (a) optionally a polymeric release matrix capable of forming a flexible film when dried, said matrix being selected from cellulose polymers or copolymers and vinylpyrrolidone/vinyl acetate copolymers, (b) an active principle, (c) a transcutaneous absorption promoter for the active principle, and (d) a physiologically acceptable non-aqueous solvent capable of dissolving the release matrix, the active principle and the transcutaneous absorption promoter, and quickly removing same by evaporation on contact with the skin. (57) Abrégé L'invention a pour objet une composition pharmaceutique pour administration transdermique caractérisée en ce qu'elle comprend (a) éventuellement une matrice polymérique de relargage capable de former un film souple après séchage, choisie parmi des polymères ou copolymères cellulosiques ou des copolymères vinylpyrrolidone/acétate de vinyle, (b) un principe actif, (c) un promoteur d'absorption transcutanée du principe actif, (d) un solvant non aqueux physiologiquement acceptable capable de dissoudre la matrice de relargage, le principe actif et le promoteur d'absorption transcutanée ainsi que de l'éliminer rapidement par évaporation au contact de la peau.		

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/EP96/04261 (22) International Filing Date: 30 September 1996 (30.09.96) (30) Priority Data: 08/535,402 28 September 1995 (28.09.95) US (71) Applicant: SCHERING AKTIENGESELLSCHAFT [DE/DE]; Müllerstrasse 178, D-13353 Berlin (DE). (72) Inventors: ELLIESEN, Jörg; Elsestrasse 12, D-13467 Berlin (DE). RIEDL, Jutta; Flensburger Strasse 14, D-10557 Berlin (DE).	(81) Designated States: AL, AU, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KE, KR, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), 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 Without international search report and to be republished upon receipt of that report.	
(54) Title: HORMONE REPLACEMENT THERAPY METHOD AND HORMONE DISPENSER (57) Abstract Varying the daily dose of either or both of the estrogen and the progestogen administered for hormone replacement therapy (HRT) is readily and inexpensively accomplished, without the necessity of the physician prescribing a new product each time the daily dose of the estrogen or progestogen is changed, by administering preferably transdermally the estrogen and progestogen contained in separate extrudable pharmaceutical compositions from a dispenser which contains means, preferably adjustable only by the attending physician or dispensing pharmacist, for varying the volume of either or both of the respective compositions which is dispensed as a single dose from the dispenser in response to a defined digital dispensing manipulation of the dispenser, thereby facilitating optimal compliance to a combination HRT with individually adjusted dosages of the estrogen and progestogen.		

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c. the pharmaceutical compositions are adapted for transdermal administration, which preferably contain a transdermal absorption enhancing agent and they are adapted to be administered by rubbing into the skin or by applying the pharmaceutical compositions to a face of a skin patch which has an adhesive surface and then adhering the patch to the skin of the patient;

d. the pharmaceutical compositions are adapted for oral ingestion and (i) the pharmaceutical compositions are viscous liquids and the delivery means is a utensil adapted to be inserted into the mouth of the female or (ii) the pharmaceutical compositions are non-sticky semi-solids and the delivery means is a hand of the female;

e. the pharmaceutical compositions are dispensed by a manually operated pump;

f. the first and second sources of the pharmaceutical compositions are separate compartments of a unitary dispenser from which individual doses of each pharmaceutical composition are extruded therefrom concurrently, either as two separate exudates or preferably as a single mixed extrudate;

g. the first and second sources each are contained in a container adapted to be opened by the attending physician for the purpose of altering the size of the individual doses of only one or of both of the estrogen and the progestogen;

h. the delivery surface is the female's hand and the estrogen and progestogen are administered to the female by rubbing the dispensed compositions onto the area of the skin where transdermal administration of the hormones is to occur;

i. the delivery surface is a sheet and the hormone-containing compositions are transferred to the skin of the female by applying thereto the face of the sheet bearing the doses of the estrogen and the progestogen, which face optionally also comprises either or both of (i) indicia which identify the respective dosages of the estrogen and progestogen which are contained in the amount of extrudate applied to that face and (ii) an adhesive area surrounding the area to which the extrudate or extrudates are applied which is adapted for adhering the sheet to the skin of the female;

j. the metered amounts of the pharmaceutical compositions are dispensed from a dispenser housing them in the first and second containers, which dispenser comprises mechanical means for changing the volume of the pharmaceutical

second containers, each of which is adapted when activated to first transfer a portion of the viscous liquid composition from the container to which the pump is connected to a metering chamber and then to discharge the metered portion from the metering chamber and from the dispenser;

n. a kit which comprises a dispenser as described in any of a) to f), above, and, as a second component, a sheet as the delivery surface;

o. a kit as described in m), above, and which has as the metering means a series of indicia on the sheet used as the delivering surface;

p. a kit comprising a dispenser as described in any of b) to l), above, which comprises a plurality of means for altering the volume of the conduit or chamber into which the pharmaceutical compositions in the dispenser are discharged for metering a single dose thereof; and wherein one of those means are mounted in or on the dispenser;

q. a kit comprising a dispenser as described in any of a) to l), above, and as a delivery surface, a sheet in the form of a skin patch with adhesive on a face thereof adapted to receive first and second compositions dispensed from the dispenser and which is adapted to be applied adhesively to the skin after the first and second compositions are applied thereto to deliver the hormones therein transdermally.

r. a kit comprising a dispenser as described in any of e) to h), j) and k) above, wherein the pharmaceutical compositions are in stick form and mounted in the dispenser in lipstick-type containers and dispensible therefrom by twisting of the base of the container, which containers preferably are removable therefrom for replacement when empty and the first and second metering means are chambers in a cap for the dispenser which limits the length of the sticks of pharmaceutical composition which can be discharged from the dispenser when the cap is mounted on the dispenser and thus the size of the single doses dispensed therefrom.

The Estrogen and Progestogen

The pharmaceutical compositions employed in the methods present in the article of manufactures of this invention comprise an estrogen and progestogen.

Examples of estrogens which can be employed in this invention (dosages shown are oral; transdermal dosages will vary therefrom in accordance with the

absorption efficacy of the vehicle employed) are ethinyl estradiol and mestranol (5 - 15 mcg/day), estradiol and their esters, e.g. valerate, acetate, benzoate and undecylate (0.5 - 4 mg/day), estriol, estriol succinate, polyestriol phosphate (2 - 8 mg), estrone, estrone sulfate and conjugated estrogens (0.3 - 1.2 mg/day). Of these, ethinyl estradiol, conjugated estrogens, estrone and especially 17 β -estradiol are preferred.

Examples of progestogens which can be employed in this invention (dosages shown are oral; transdermal dosages will vary therefrom in accordance with the adsorption efficacy of the vehicle employed) are micronized progesterone (100 - 200 mg/day), norethisterone and esters, e.g., acetate (0.5 - 2 mg/day), thereof, norgestrel (80 - 250 mcg/day), levo-norgestrel (40 - 125 mcg/day), chlormadinone acetate (1 - 2 mg/day), cyproterone acetate (1 - 2 mg/day), desogestrel, 3-ketodesogestrel (40 - 120 mcg/day), drospirenone (1 - 3 mg/day), norgestimate, or gestodene (20 - 80 mcg/day).

Of these, gestodene, levo-norgestrel, 3-ketodesogestrel, drospirenone and especially gestodene, levo-norgestrel and 3-ketodesogestrel are preferred.

The pharmaceutical compositions of this invention contain, for example, 17 β -estradiol in a 2 % concentration or levo-norgestrel for example in a 1 % concentration or a biologically equivalent concentration of another estrogen or progestogen, respectively. Amounts of 0.25 - 1 g of each of the compositions would be sufficient to ensure the release and absorption of minimum daily therapeutic amounts approximately equal to 50 mcg of 17 β -estradiol and approximately 40 mcg of levo-norgestrel.

The Pharmaceutical Compositions

The pharmaceutical compositions employed in the method of this invention and present in the dispensers of this invention contain the multiple doses of the estrogen or the gestagen in non-discreet form so that individual doses of any desired size can be dispensed therefrom, i.e., they are an extrudable viscous liquid, e.g., one which will flow after being transferred to the delivery surface, or

an extrudable semi-solid, e.g., a gel, ointment or creme which is dimensionally stable on the delivery surface, during the period between extrusion and application to the skin, or a spreadable solid, similar to a stick deodorant. When the composition is a viscous liquid, it preferably has a viscosity of 2,000-100,000 cps, more preferably 5,000-50,000 cps, so that it can be dispensed by a lotion-type pump dispenser and administered by spreading onto the skin by rubbing (topical administration). When the composition is a semisolid it preferably has a viscosity of 50,000-500,000 cps so that it can be extruded as a pasty mass and administered by either the oral or transdermal route. The compositions preferably have micropenetration values of less than $1000\text{mm} \times 10^{-1}$, preferably more than $1000\text{mm} \times 10^{-1}$. Measured by another method (extensometer test) the extensometer values are in the range of from 200mm^2 (more viscous) to 4000mm^2 (more fluid), preferably more than 4000mm^2 . As will be appreciated by those skilled in the art, there is no clear distinction between a very viscous extrudable liquid and a very soft extrudable semi-solid. For the purposes of this invention, they are both suitable.

The vehicle in which the estrogen or progestogen is dissolved or suspended can be aqueous, if the selected hormone therein is storage-stable, or nonaqueous, e.g., ethanol or methanol, and can contain one or more of the pharmaceutical carriers, adjuvants or excipients conventionally employed in a composition adapted for transdermal drug administration, and include any such materials known in the art, e.g., any liquid, gel, solvent, liquid diluent, solubilizer, or the like, which is nontoxic and which does not interact with other components of the composition in a deleterious manner. Examples of suitable adjuvants are water, liquid glyceryl triesters with low molecular weight fatty acids or wax-like esters, lower alkanols, natural oils such as corn oil, groundnut oil, sesame oil, castor oil or condensation products thereof with ethylene oxide, and the like, hydrocarbons such as pharmaceutical grade mineral oil, silicones, emulsifiers such as monoglycerides or diglycerides of fatty acids, phospholipic acid derivatives such as lecithin or cephalin, polyalkylene glycols such as polyethylene glycol, aqueous phases to which a swelling agent such as sodium carboxymethylcellulose, sodium alginate, polyvinylpyrrolidone, etc., has been added and to which, in addition, dispersion agents or emulsifiers such as lecithin may be added, polyoxyethylene-derivatives and the like. The adjuvants may, in addition, contain additives such as preservatives, stabilizers, wetting agents, emulsifiers, etc. The composition

preferably also contains a transdermal absorption enhancing agent, which can also serve as a carrier component. When the composition is a semi-solid, a conventional extrusion assist agent which reduces the energy required to extrude the composition preferably is present.

Although this invention employs, in a preferred embodiment, a pharmaceutical composition adapted for HRT transdermal self-administration of an estrogen and a progestogen, it will be apparent to those skilled in the art that the principle upon which this invention is based, viz., the use of pharmaceutical compositions containing a plurality of doses of an estrogen and a progestogen in non-unitary dosage form, i.e., an extrudable semi-solid or a viscous liquid as opposed to a tablet, pill, dragee or transdermal patch containing a single dose of the estrogen and of progestogen, in combination with a dispensing means whereby the individual dosage of each of the hormones and preferably also the ratio thereof can be varied by making an adjustment in the dispensing means, can be used in oral therapy by use of an appropriate vehicle for the hormones which is adapted for ingestion and a transport composition suitable for introduction into the mouth, e.g., a spoon with volume indicia for measuring the doses.

Topical Compositions

The pharmaceutical compositions employed in the method of this invention and in the dispensers of this invention are preferably administered by application to an appropriate area of the skin (or mucosa). Therefore, they preferably contain an effective amount of an absorption enhancing agent.

The term "topical" as used herein embraces both transdermal and transmucosal administration.

The term "effective" amount when used herein with respect to a topical absorption (or permeation) enhancing agent means an amount that effects a significant increase in the permeability of the area of the skin or mucosa to which the pharmaceutical compositions of this invention are applied and, correspondingly, the desired depth of penetration, rate of administration, and amount of drug delivered systemically.

Examples of absorption enhancing agents are those described in PCT/US90/01469, viz., a mixture having as a first ether component a diethylene glycol monoethyl or monomethyl ether, or both, e.g., the commercially available

WHAT IS CLAIMED IS:

1. An HRT method of self-administration by a human female of successive doses of an estrogen and a plurality of successive doses of a progestogen, wherein the female dispenses and self-administers successive individual doses of the estrogen and of the progestogen over a protracted period of time, during which period of time the amount of at least one of which doses is changed, which method comprises the steps of:

a) dispensing to a delivery surface, from a first source of a first semisolid or viscous liquid pharmaceutically acceptable composition containing a plurality of non-discrete doses of the estrogen, a metered volume of the first composition as a single dose of the estrogen;

b) concurrently dispensing to the delivery surface, from a second source of a second semisolid or viscous liquid pharmaceutically acceptable composition containing a plurality of non-discrete doses of the progestogen, a metered volume of the second composition as a single dose of the progestogen;

c) transporting the dispensed doses of the first and second compositions from the delivery surface simultaneously to the site of administration of the estrogen and progestogen and administering the dispensed estrogen and progestogen thereat;

d) repeating steps a) - c) on a predetermined schedule; and

e) periodically, in response to the physiological symptoms associated with menopause or the HRT currently exhibited by the female, changing the metered volume of at least one of the first and second compositions which is dispensed onto the delivery surface as a single dose thereof.

2. A method according to claim 1, wherein the predetermined schedule of Step d) is daily.

3. A method according to claim 1, wherein the site of administration is an area of the skin of the female and the first and second pharmaceutically acceptable compositions are adapted to transdermal administration.

4. A method according to claim 3, wherein the delivery surface is the female's hand and the compositions thereon are administered at the selected site of transdermal administration on the skin of the female by rubbing the hand against the skin.

5. A method according to claim 1, wherein the pharmaceutical compositions are semi-solids which are dispensed as extrudates.

6. A method according to claim 1, wherein the first and second pharmaceutically acceptable compositions are dispensed simultaneously from the respective sources thereof.

7. A method according to claim 1, wherein the dispensed doses of the first and second pharmaceutically acceptable compositions are mixed before being dispensed onto the delivery surface.

8. A method according to claim 1, wherein the predetermined schedule of Step d) is daily; wherein the site of administration is the skin of the female and the first and second pharmaceutically acceptable compositions are adapted to transdermal administration; wherein the compositions thereon are delivered to the selected site of transdermal administration on the skin of the female by rubbing; wherein the pharmaceutical compositions are semi-solids and are dispensed as extrudates simultaneously from the respective sources thereof; and wherein the metered doses of the first and second pharmaceutically acceptable compositions are mixed before being extruded onto the delivery surface.

9. A method according to claim 1, wherein the source of the first pharmaceutical composition is a first compartment of a unitary dispensing means and the source of the second pharmaceutical composition is a second compartment of the dispensing means; wherein the first and second pharmaceutical compositions are first extruded from their respective compartments into first and second metering chambers, respectively; and wherein the contents of the metering chambers are then formed into a single extrudate which is then dispensed from the dispensing means.

10. A method according to claim 1, wherein either the length of the extrudates of the first and second pharmaceutical compositions which are extruded from the respective sources thereof is constant and the dosage of the hormones therein is changed in Step (e) by changing the diameter of one or both of the extrudates, or wherein the diameter of the extrudates of the first and second pharmaceutical compositions which are extruded from the respective sources thereof is constant and the dosage of the hormones therein is changed in Step (e) by changing the length of one or both of the extrudates.

11. A method according to claim 1, wherein the estrogen is ethinyl estradiol or estradiol or an ester thereof, estrone, estrone sulfate or conjugated estrogens and the progestogen is micronized progesterone, norethindrone or esters thereof, norgestrel, chlormadinone acetate, cyproterone acetate, desogestrel, 3-ketodesogestrel, drospirenone, norgestimate, levo-norgestrel or gestodene.

12. A method according to claim 1, wherein the estrogen is ethinyl estradiol or 17 β -estradiol and the progestogen is gestodene, levonorgestrel or 3-ketodesogestrel.

13. A method according to claim 12, wherein the predetermined schedule of Step d) is daily; wherein the pharmaceutical compositions are semi-solids; wherein the pharmaceutical compositions are metered from a dispenser in which the first and second containers both are housed, which the dispenser comprises mechanical means for changing the volumes of the pharmaceutical compositions which are dispensed from the containers in response to a defined constant digital manipulation employed to extrude from the container.

14. A dispenser adapted for dispensing and self-administering a plurality of successive individual doses of an estrogen and a progestogen from a dispenser containing multiple doses of thereof in separate extrudable pharmaceutically acceptable compositions, in metered single dosage amounts which can be varied by mechanically modifying the dispenser, which comprises:

a) a first container comprising:

(i) a first chamber containing a plurality of doses of the estrogen in a first extrudable pharmaceutically acceptable composition;

(ii) a discharge port through which a volume of the first pharmaceutical composition in the first chamber can be discharged therefrom when discharging pressure is applied to the first container;

(iii) means for applying discharging pressure to the first chamber;

b) a second container comprising:

(i) a second chamber containing a plurality of doses of the progestogen in a second extrudable liquid pharmaceutically acceptable composition;

(ii) a discharge port through which a volume of the second extrudable pharmaceutical composition in the second chamber can be discharged therefrom when discharging pressure is applied to the second container;

(iii) means for applying discharging pressure to the second chamber;

c) a first metering means adapted to receive a volume of the first extrudable pharmaceutical composition extruded thereinto from the first chamber and digitally reciprocally convertible from a receiving mode, where it communicates with the first chamber through the first port and where it can be filled with a volume of the first extrudable pharmaceutical composition, to a discharging mode, where a volume of the first extrudable pharmaceutical composition therein can be discharged therefrom and dispensed from the dispenser, which first metering means comprises:

(i) a first adjusting means for varying the volume of the first extrudable pharmaceutical composition which can be extruded thereinto;

d) a second metering means adapted to receive a volume of the second extrudable pharmaceutical composition extruded thereinto from the second chamber and digitally reciprocally convertible from a receiving mode, where it communicates with the second chamber through the second port and where it can be filled with a volume of the second extrudable pharmaceutical composition, to a discharging mode, where a volume of the second extrudable pharmaceutical composition therein can be discharged therefrom and dispensed from the dispenser, which second metering means comprises:

(i) a second adjusting means for varying the volume of the second extrudable pharmaceutical composition which can be extruded thereinto as a single dose of the progestogen; and

e) dispensing means for dispensing a volume of the first pharmaceutical composition and a volume of the second pharmaceutical composition from the first and second metering means, respectively, from the dispenser as a single dose of the estrogen and the progestogen.

15. A dispenser according to claim 14 which comprises means for blending the single dose of the estrogen and the single dose of the progestogen discharged from the first and second metering means into a single extrudate prior to being dispensed from the dispenser.

16. A dispenser according to claim 14, wherein the first and second adjusting means are positioned internally in the dispenser and not readily accessible by an individual dispensing single doses of the estrogen and the progestogen therefrom.

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17. A dispenser according to claim 14, wherein the estrogen is ethinyl estradiol or estradiol or an ester thereof, estrone, estrone sulfate or conjugated estrogens and the progestogen is micronized progesterone, norethindrone or esters thereof, norgestrel, chlormadinone acetate, cyproterone acetate, desogestrel, 3-ketodesogestrel, drospirenone, norgestimate, levo-norgestrel or gestodene.

18. A dispenser according to claim 14, wherein the estrogen is ethinyl estradiol or 17 β -estradiol and the progestogen is gestodene, levonorgestrel or 3-ketodesogestrel.

19. A dispenser according to claim 18, which comprises means for blending the single dose of the estrogen and the single dose of the progestogen discharged from the first and second metering means into a single extrudate prior to being dispensed from the dispenser, wherein the estrogen is ethinyl estradiol or 17 β -estradiol, the progestogen is gestodene, levonorgestrel or 3-ketodesogestrel.

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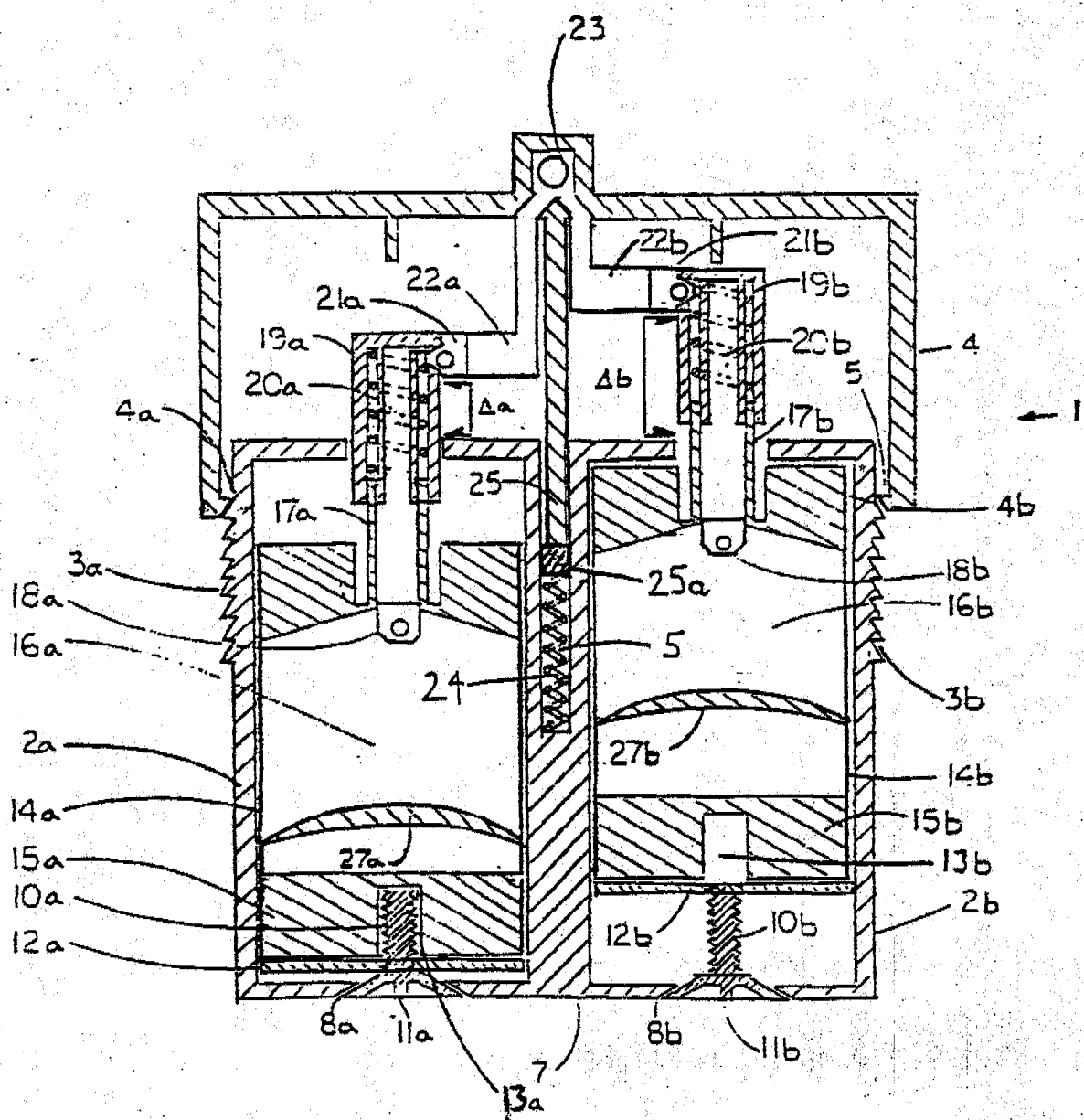


FIG. 1

SUBSTITUTE SHEET (RULE 26)



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199**United States Patent** [19]

Spona et al.

[11] **Patent Number:** 5,583,129[45] **Date of Patent:** Dec. 10, 1996[54] **COMPOSITION FOR CONTRACEPTION**

[76] **Inventors:** Jürgen Spona, Billrothstrasse 78, A-1190 Vienna, Austria; Bernd Düsterberg, Spirdingseestrasse 27, D-12307 Berlin, Germany; Frank Lüdicke, c/o Hopital Cantonal Universitaire, 32bis, Blvd de la Cluse, CH-1211 Geneva 4, Switzerland

A. R. Genazzani, et al. (Ed), Progress in Gynecology and Obstetrics, "Multicenter Clinical Trial on the new Oral Contraceptive 20 µg Ethinylestradiol", Chapter 1, pp. 747-756, (1990).

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A61K 31/585[52] **U.S. Cl.** 514/178; 514/173; 514/182[58] **Field of Search** 514/178, 182,
514/173[56] **References Cited****FOREIGN PATENT DOCUMENTS**

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[57] **ABSTRACT**

This invention relates to a method of inducing contraception comprising administering an estrogen selected from

2.0 to 6.0 mg of 17β-estradiol and
0.015 to 0.020 mg of ethinylestradiol;
and a gestagen selected from
0.05 to 0.075 mg of gestodene,
0.075 to 0.125 mg of levonorgestrel,
0.06 to 0.15 mg of desogestrel,
0.06 to 0.15 mg of 3-ketodesogestrel,
0.1 to 0.3 mg of drospirenone,
0.1 to 0.2 mg of cyproterone acetate,
0.2 to 0.3 mg of norgestimate and
>0.35 to 0.75 mg of norethisterone

for a female of reproductive age, who has not yet reached premenopause, by administration for 23 or 24 days, beginning on day one of the menstrual cycle, followed by 5 or 4 pill-free or sugar pill days, during a total of 28 days in the administration cycle.

8 Claims, 1 Drawing Sheet



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(21) International Application Number: PCT/EP96/04261 (22) International Filing Date: 30 September 1996 (30.09.96) (30) Priority Data: 08/535,402 28 September 1995 (28.09.95) US (71) Applicant: SCHERING AKTIENGESELLSCHAFT [DE/DE]; Müllerstrasse 178, D-13353 Berlin (DE). (72) Inventors: ELLIEN, Jörg; Elsestrasse 12, D-13467 Berlin (DE). RIEDL, Jutta; Flensburger Strasse 14, D-10557 Berlin (DE).	(81) Designated States: AL, AU, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KE, KR, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), 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, BI, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published Without international search report and to be republished upon receipt of that report.	
(54) Title: HORMONE REPLACEMENT THERAPY METHOD AND HORMONE DISPENSER		
(57) Abstract		
Varying the daily dose of either or both of the estrogen and the progestogen administered for hormone replacement therapy (HRT) is readily and inexpensively accomplished, without the necessity of the physician prescribing a new product each time the daily dose of the estrogen or progestogen is changed, by administering preferably transdermally the estrogen and progestogen contained in separate extrudable pharmaceutical compositions from a dispenser which contains means, preferably adjustable only by the attending physician or dispensing pharmacist, for varying the volume of either or both of the respective compositions which is dispensed as a single dose from the dispenser in response to a defined digital dispensing manipulation of the dispenser, thereby facilitating optimal compliance to a combination HRT with individually adjusted dosages of the estrogen and progestogen.		

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 WELTORGANISATION FÜR GEISTIGES EIGENTUM
 Internationales Büro
 INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE
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(51) Internationale Patentklassifikation 6 : A61K 31/57, 31/565	A1	(11) Internationale Veröffentlichungsnummer: WO 95/17194 (43) Internationales Veröffentlichungsdatum: 29. Juni 1995 (29.06.95)
(21) Internationales Aktenzeichen: PCT/EP94/04274 (22) Internationales Anmeldedatum: 22. December 1994 (22.12.94) (30) Prioritätsdaten: P 43 44 462.8 22. December 1993 (22.12.93) DE (71) Anmelder: SCHERING AKTIENGESELLSCHAFT [DE/DE]; Müllerstrasse 178, D-13353 Berlin (DE). (72) Erfinder: SPONA, Jürgen; Bilkrothstrasse 78, A-1190 Wien (AT). DÜSTERBERG, Bernd; Spirdingseestrasse 27, D- 12307 Berlin (DE). LÜDICKE, Frank; Hôpital Cantonal Universitaire, Clinic of Sterility and Gynaecologic En- docrinology, 32bis, boulevard de la Cluse, CH-1211 Geneva 4 (CH). FRICHTINGER, W.; Trautmansdorffgasse 3a, A- 1130 Wien (AT). ELSTEIN, Max; University of Manches- ter, Dept. of Obstetrics & Gynecology, Nell Lane, West Didsbury, Manchester M20 8LR (GB).	(81) Bestimmungsstaaten: CA, CN, CZ, HU, JP, KR, LT, LV, NO, NZ, PL, RU, SI, SK, UA, europäisches Patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Veröffentlicht <i>Mit internationalem Recherchenbericht. Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.</i>	
(54) Title: COMPOSITION FOR A CONTRACEPTIVE COMPRISING AN ESTROGEN AND A GESTAGEN. (54) Bezeichnung: ZUSAMMENSETZUNG FÜR DIE EMPFÄNGNISVERHÜTUNG UMFASSEND EIN ESTROGEN UND EIN GESTAGEN (57) Abstract The invention concerns the use of a composition comprising an estrogen selected from 2.0-6.0 mg 17β-estradiol and 0.015-0.020 mg ethinyl estradiol and a gestagen selected from 0.05-0.075 mg gestodene, 0.075-0.125 mg levonorgestrel, 0.06-0.15 mg desogestrel, 0.06-0.15 mg 3-ketodesogestrel, 0.1-0.3 mg drospirenone, 0.1-0.2 mg cyproterone acetate, 0.2-0.3 mg norgestimate and >0.35-0.75 mg norethisterone, used to produce a dosage formulation for contraception for a woman of child-bearing age who has not reached premenopause by administering the dosage formulation during 23 or 24 days, beginning on day one of the menstrual cycle, followed by 5 or 4 pill-free or placebo days, over a complete 28-day cycle of administration, wherein the individual dosage formulations contain a constant amount of estrogen/gestagen throughout the 23 or 24 days. The invention also pertains to a combination oral contraceptive based on this composition. (57) Zusammenfassung Die vorliegende Erfindung betrifft die Verwendung einer Zusammensetzung umfassend ein Estrogen ausgewählt aus 2,0 bis 6,0 mg 17β-Estradiol und 0,015 bis 0,020 mg Ethinylestradiol; und ein Gestagen ausgewählt aus 0,05 bis 0,075 mg Gestoden, 0,075 bis 0,125 mg Levonorgestrel, 0,06 bis 0,15 mg Desogestrel, 0,06 bis 0,15 mg 3-Ketodesogestrel, 0,1 bis 0,3 mg Drospirenon, 0,1 bis 0,2 mg Cyproteronacetat, 0,2 bis 0,3 mg Norgestimat und >0,35 bis 0,75 mg Norethisteron zur Herstellung einer Dosierungsform für die Empfängnisverhütung für eine Frau im fertilen Alter, die die Prämenopause noch nicht erreicht hat, durch Verabreichung der Dosierungsform während 23 oder 24 Tagen, beginnend am Tag eins des Menstruationszyklus, gefolgt von 5 oder 4 pillenfreien oder Blindpillentagen, während insgesamt 28 Tagen im Verabreichungszyklus, wobei die einzelnen Dosierungsformen über alle 23 oder 24 Tage eine konstante Estrogen/Gestagenmenge enthalten, sowie ein monophasisches Kombinationsprodukt für die orale Kontrazeption auf der Basis dieser Zusammensetzung.		

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/58, 31/57, 31/565	A1	(11) International Publication Number: WO 98/04269 (43) International Publication Date: 5 February 1998 (05.02.98)
(21) International Application Number: PCT/US97/12795 (22) International Filing Date: 23 July 1997 (23.07.97) (30) Priority Data: 08/686,790 26 July 1996 (26.07.96) US (71) Applicant: AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Giralda Farms, Madison, NJ 07940-0874 (US). (72) Inventor: GAST, Michael, Jay; 230 Country Lane, Phoenixville, PA 19460 (US). (74) Agents: ALICE, Ronald, W.; American Home Products Corporation, Patent Law Dept. - 2B, One Campus Drive, Parsippany, NJ 07054 (US) et al.	(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> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: MONOPHASIC CONTRACEPTIVE METHOD AND KIT COMPRISING A COMBINATION OF A PROGESTIN AND ESTROGEN		
(57) Abstract This invention provides a method of contraception which comprises administering to a female of child bearing age for a combination of a progestin at a daily dosage of 40-500 μg trimenopristone, 250 μg - 4 mg dienogest, or 250 μg - 4 mg drospirenone, and an estrogen at a daily dosage equivalent in estrogenic activity to 10-20 μg ethinyl estradiol for 23-25 days beginning on day 1 of the menstrual cycle, and wherein the same dosage of the progestin and estrogen combination is administered in each of the 23-25 days.		



US005858405A

United States Patent [19]

Gast

[11] Patent Number: 5,858,405

[45] Date of Patent: *Jan. 12, 1999

[54] ORAL CONTRACEPTIVE

[75] Inventor: Michael J. Gast, Phoenixville, Pa.

[73] Assignee: American Home Products Corporation, Madison, N.J.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,747,480.

[21] Appl. No.: 887,162

[22] Filed: Jul. 2, 1997

Related U.S. Application Data

[60] Provisional application No. 60/022,624 Jul. 26, 1996.

[51] Int. Cl. ⁶ A61K 9/20; A61K 31/56

[52] U.S. Cl. 424/464; 514/170; 514/841; 514/843

[58] Field of Search 424/464; 514/170; 514/841, 843

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Primary Examiner—Thurman K. Page

Assistant Examiner—James M. Spear

Attorney, Agent, or Firm—Arnold S. Milowsky

[57] ABSTRACT

This invention provides a bridged triphasic combination progestin/estrogen oral contraceptive regimen comprising the administration of a contraceptive progestin/estrogen combination for 23-25 days consecutive days beginning on the first day of menses, followed by the administration of an estrogen for 3-5 days following the administration of the estrogen/progestin combination, so that the total period of administration is 28 days per 28 day cycle. Particularly preferred progestins of this invention are trimegestone, dienogest, and drospirenone.

20 Claims, No Drawings

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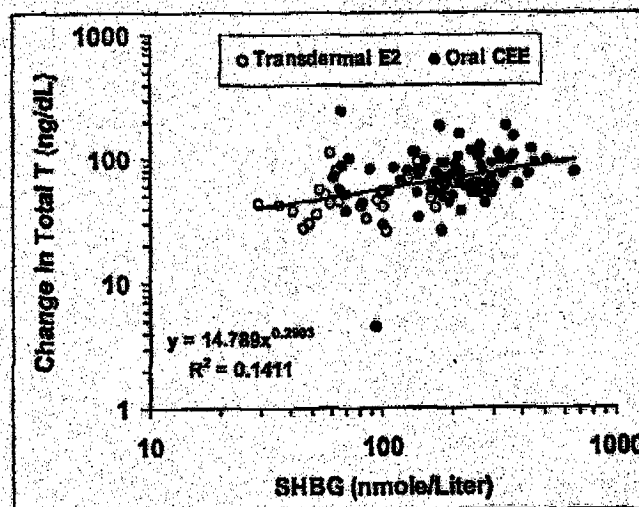
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- (51) International Patent Classification⁷: A61K 31/56 (74) Agents: WESTERN, M., Wayne et al.; Thorpe, North & Western, LLP, P.O. Box 1219, Sandy, UT 84091-1219 (US).
- (21) International Application Number: PCT/US00/15834
- (22) International Filing Date: 9 June 2000 (09.06.2000) (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.
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60/139,323 11 June 1999 (11.06.1999) US
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- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:
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[Continued on next page]

(54) Title: ADMINISTRATION OF NON-ORAL ANDROGENIC STEROIDS TO WOMEN



(57) Abstract: The present invention provides compositions, methods, and kits for improving health in a woman having elevated sex hormone binding globulin (SHBG) levels, or who is receiving oral estrogen supplementation, by non-orally administering an effective amount of an androgenic steroid. Further, the present invention provides compositions, methods and kits for coadministering an effective amount of an orally administered estrogen and an effective amount of a non-orally administered androgenic steroid for women in need of estrogen supplementation. Fig. 1 shows the change in total testosterone level versus baseline SHBG level during application of transdermal testosterone patch (300 mcg/day nominal delivery) to patients concomitantly receiving transdermal estradiol or oral conjugated equine estrogens. Fig. 2 shows the change in free testosterone level versus baseline SHBG level during application of transdermal testosterone patch (300 mcg/day nominal delivery) to patients concomitantly receiving transdermal estradiol or oral conjugated equine estrogens.

WO 00/76522 A1



US006071531A

United States Patent [19]

Jona et al.

[11] Patent Number: 6,071,531

[45] Date of Patent: Jun. 6, 2000

[54] TRANSDERMAL PATCH AND METHOD FOR ADMINISTERING 17-DEACETYL NORGESTIMATE ALONE OR IN COMBINATION WITH AN ESTROGEN

[75] Inventors: Janan Jona, Sunnyvale; Jay Audett, Mountain View; Noel Singh, San Francisco, all of Calif.

[73] Assignee: Ortho-McNeil Pharmaceutical, Inc., Raritan, N.J.

[21] Appl. No.: 09/340,859

[22] Filed: Jun. 28, 1999

Related U.S. Application Data

[63] Continuation of application No. 09/165,526, Oct. 2, 1998, which is a continuation of application No. 08/660,024, Jun. 6, 1996, Pat. No. 5,876,746, which is a continuation-in-part of application No. 08/517,263, Aug. 21, 1995, which is a continuation-in-part of application No. 08/473,531, Jun. 7, 1995.

[51] Int. Cl.⁷ A61M 37/00

[52] U.S. Cl. 424/449; 424/448

[58] Field of Search 424/449, 448; 604/307; 514/947

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Primary Examiner—Edward J. Webman

[57] ABSTRACT

Compositions and methods for preventing ovulation in a woman are provided, as well as compositions and methods for female hormone replacement therapy. The compositions can be administered by the use of a transdermal patch. The patch will administer 17-deacetyl norgestimate alone or in combination with an estrogen such as ethinyl estradiol to women.

25 Claims, No Drawings

(19)



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(54) **PRESERVATIF EQUIPE D'UNE PASTILLE RIGIDE DETROMPEUSE ET DE PROTECTION**
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(56) Documents cités:
WO-A-90/12554 DE-A- 3 902 093
DE-U- 8 914 151 US-A- 2 904 041

Il est rappelé que: Dans un délai de neuf mois à compter de la date de publication de la mention de la délivrance du brevet européen, toute personne peut faire opposition au brevet européen délivré, auprès de l'Office européen des brevets. L'opposition doit être formée par écrit et motivée. Elle n'est réputée formée qu'après paiement de la taxe d'opposition. (Art. 99(1) Convention sur le brevet européen).



US005798347A

United States Patent [19]

Labrie

[11] Patent Number: 5,798,347

[45] Date of Patent: Aug. 25, 1998

[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.: 477,170

[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

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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.

10 Claims, 9 Drawing Sheets

(19)



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accordance with Art. 76 EPC: 91912052.7

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Remarks:

This application was filed on 06 - 06 - 1996 as a
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under INID code 62.

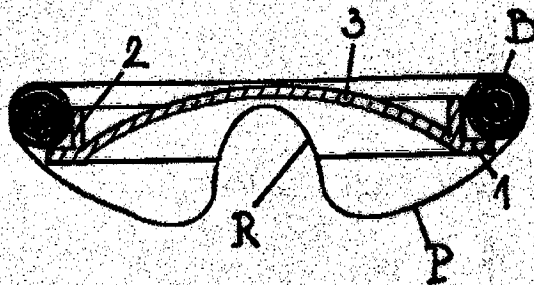
(54) **Topical application of ST1435 as a contraceptive agent**

(57) The progesterone analog 17 α -acetoxy-16-methylene-19-norprogesterone (ST1435) has now been found to attain contraceptively effective levels upon topical application to the skin. ST1435 can be administered topically either in liquid or semisolid base such as a cream or gel or in a solid base such as a transdermal device such as a disk, band, patch or bracelet.

ST-1435 is useful to treat benign breast disease by topical application.

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DEMANDE INTERNATIONALE PUBLIÉE EN VERTU DU TRAITÉ DE COOPÉRATION EN MATIÈRE DE BREVETS (PCT)

(51) Classification internationale des brevets ⁵ : A61F 6/04	A1	(11) Numéro de publication internationale: WO 94/05237 (43) Date de publication internationale: 17 mars 1994 (17.03.94)
(21) Numéro de la demande internationale: PCT/FR93/00737 (22) Date de dépôt international: 20 juillet 1993 (20.07.93) (30) Données relatives à la priorité: 92/10353 28 août 1992 (28.08.92) FR (71)(72) Déposant et inventeur: BABLED, Raymond [FR/FR]; 72, avenue d'Orgeval, F-95210 Saint-Gratien (FR). (81) Etats désignés: JP, KR, US, brevet européen (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).		Publiée <i>Avec rapport de recherche internationale.</i>
(54) Title: PROTECTION AND UNDECEITFUL RIGID PATCH FOR CONTRACEPTIVE SHEATH; CONTRACEPTIVE SHEATH PROVIDED WITH SUCH PATCH		
(54) Titre: PASTILLE RIGIDE DETROMPEUSE ET DE PROTECTION POUR PRÉSERVATIF; PRÉSERVATIF ÉQUIPE D'UNE TELLE PASTILLE		
		
(57) Abstract Protection and undecetful rigid patch for contraceptive sheath, having on its contour a flat flange (1) intended to be engaged under the winding bead (B) of the contraceptive sheath (P), said patch being arranged on the extremity and on the external side of the sheath. The flange (1) surrounds a portion of said patch which presents externally an overthickness with respect to the plane of the flange. Said overthickness is preferably comprised of a lateral bearing skirt (2) surrounding a convex bottom (3) which may be spherical. Application to all contraceptive sheaths.		
(57) Abrégé Pastille rigide détrompeuse et de protection pour préservatif, ayant sur son pourtour une collerette plate (1) destinée à être engagée sous le bourrelet d'enroulement (B) du préservatif (P), ladite pastille étant disposée sur l'extrémité et du côté extérieur de celui-ci. La collerette (1) entoure une partie de ladite pastille qui, vers l'extérieur, présente une surépaisseur par rapport au plan de la collerette. Cette surépaisseur comporte de préférence une jupe d'appui latéral (2) entourant un fond convexe (3), par exemple sphérique. Application à tous préservatifs.		

United States Patent [19]
Campbell et al.

[11] Patent Number: 4,460,372
[45] Date of Patent: Jul. 17, 1984

[54] PERCUTANEOUS ABSORPTION
ENHANCER DISPENSER FOR USE IN
COADMINISTERING DRUG AND
PERCUTANEOUS ABSORPTION
ENHANCER

4,060,084 11/1977 Chandrasekaran 604/897
4,096,239 6/1978 Katz et al. 424/21
4,230,105 10/1980 Harwood 128/156
4,286,592 9/1981 Chandrasekaran 128/156
4,291,014 9/1981 Keith et al. 424/28

[75] Inventors: Patricia S. Campbell; Santosh K.
Chandrasekaran, both of Palo Alto,
Calif.

Primary Examiner—Benjamin R. Padgett

Assistant Examiner—T. J. Wallen

Attorney, Agent, or Firm—Steven F. Stone; Edward L.
Mandell; Paul L. Sabatine

[73] Assignee: ALZA Corporation, Palo Alto, Calif.

[21] Appl. No.: 481,209

[22] Filed: Apr. 1, 1983

[57] ABSTRACT

A dosage form that coadministers a drug and a percutaneous absorption enhancer to a defined area of the skin. The dosage form comprises a body that contains supplies of drug and enhancer and has a basal surface that contacts the area of skin and transmits the drug and enhancer to the area for absorption thereby. The drug is provided to the basal surface at a rate at least as great as the rate at which the skin is able to absorb the drug whereas the enhancer is via a rate controlling means at a substantially constant rate that increases the permeability of the treated area of skin to the drug to a level at which the drug is absorbed a therapeutically effective rate.

Related U.S. Application Data

[63] Continuation of Ser. No. 235,068, Feb. 17, 1981, Pat.
No. 4,379,454.

[51] Int. Cl. A61M 7/00

[52] U.S. Cl. 604/897

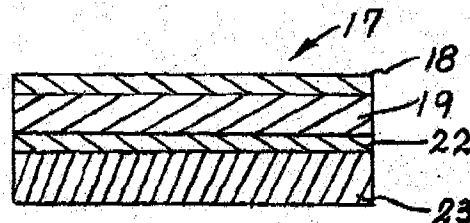
[58] Field of Search 604/890-897;
424/22-28; 128/155, 156

[56] References Cited

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11 Claims, 9 Drawing Figures





US005858405A

United States Patent [19][11] **Patent Number:** 5,858,405**Gast**[45] **Date of Patent:** *Jan. 12, 1999[54] **ORAL CONTRACEPTIVE**[75] **Inventor:** Michael J. Gast, Phoenixville, Pa.[73] **Assignee:** American Home Products Corporation, Madison, N.J.[*] **Notice:** The term of this patent shall not extend beyond the expiration date of Pat. No. 5,747,480.[21] **Appl. No.:** 887,162[22] **Filed:** Jul. 2, 1997**Related U.S. Application Data**[60] **Provisional application No.** 60/022,624 Jul. 26, 1996.[51] **Int. Cl. ⁶** A61K 9/20; A61K 31/56[52] **U.S. Cl.** 424/464; 514/170; 514/841; 514/843[58] **Field of Search** 424/464; 514/170; 514/841, 843[56] **References Cited****U.S. PATENT DOCUMENTS**

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OTHER PUBLICATIONS

Sartoretto et al., Clinical evaluation of a low dosage estrogen-progesterone association (100µg of d-norgestrel and 20µg ethinyl [sic] estradiol), Clinica e Terapeutica (1974) 3:399-404.

Primary Examiner—Thurman K. Page

Assistant Examiner—James M. Spear

Attorney, Agent, or Firm—Arnold S. Milowsky

[57] **ABSTRACT**

This invention provides a bridged triphasic combination progestin/estrogen oral contraceptive regimen comprising the administration of a contraceptive progestin/estrogen combination for 23–25 days consecutive days beginning on the first day of menses, followed by the administration of an estrogen for 3–5 days following the administration of the estrogen/progestin combination, so that the total period of administration is 28 days per 28 day cycle. Particularly preferred progestins of this invention are trimegestone, dienogest, and drospirenone.

20 Claims, No Drawings

2020
Bogotá, D.C.,

Doctor:
Ian Raisbeck Llinas
Apoderado

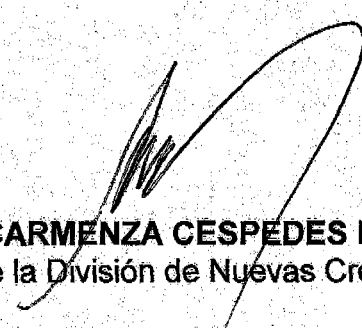
Oficio N°: 4945

ASUNTO:	Radicación PCT N°	06-110229
	Trámite	011
	Evento	379
	Actuación	440
	Folios	011

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por la doctora Laura Catalina Silva Barrera, en su calidad de apoderada de Procaps S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

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 CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior oficio fue notificado por fijación en lista de fecha, 17 ABR 2008.

202021

Peter Coon Instals
David Hillman

2020
Bogotá, D.C.,

Doctor:
Ian Raisbeck Llinas
Apoderado

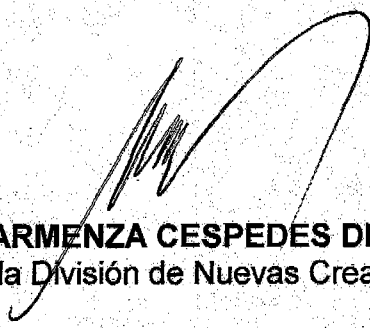
Oficio N°: 4947

ASUNTO:	Radicación PCT N°	06-110229
	Trámite	011
	Evento	379
	Actuación	440
	Folios	054

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado del Laboratorio Franco Colombiano Lafranco S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

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 CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior oficio fue notificado por fijación en lista de fecha, 11 ABR 2008.

202021



US 20030144258A1

214
217
D-1(19) **United States**(12) **Patent Application Publication** (10) **Pub. No.: US 2003/0144258 A1****Heil et al.**(43) **Pub. Date:****Jul. 31, 2003**(54) **DROSPIRENONE FOR HORMONE
REPLACEMENT THERAPY****Publication Classification**(75) **Inventors:** Wolfgang Heil, Berlin (DE); Juergen
Hilmann, Berlin (DE); Ralph Lipp,
Berlin (DE); Rolf Schuermann, Berlin
(DE)(51) **Int. Cl.⁷** A61K 31/56; A61K 31/585
(52) **U.S. Cl.** 514/170; 514/182**Correspondence Address:****MILLEN, WHITE, ZELANO & BRANIGAN,
P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201 (US)**(57) **ABSTRACT**(73) **Assignee:** Schering Aktiengesellschaft, Berlin
(DE)(21) **Appl. No.:** 10/359,085(22) **Filed:** Feb. 6, 2003**Related U.S. Application Data**(62) **Division of application No. 09/757,688, filed on Jan.
11, 2001.**

A pharmaceutical composition comprising as a first active ingredient an estrogen, such as estradiol or estradiol valerate, in sufficient amounts to treat disorders and symptoms associated with deficient endogenous levels of estrogen in women, and as a second active ingredient 6 β ,7 β , 15 β , 16 β -dimethylene-3-oxo-17 α -preg-4-ene-21,17-carbolactone (drospirenone, DRSP) in sufficient amounts to protect the endometrium from the adverse effects of estrogen is useful for, amongst others, treating peri-menopausal, menopausal and post-menopausal women. This composition may be used for hormone replacement therapy and may be administered as a multi-phased pharmaceutical preparation. This combination therapy may comprise continuous, sequential or interrupted administration, or combinations thereof, of DRSP and estrogen, each optionally in micronized form.

EXAMPLE 6: Menopausal Symptoms

[0119] Objective: To demonstrate that the therapeutic efficacy of E2-DRSP regarding menopausal symptoms is superior to placebo.

[0120] Primary Objective: Hot flashes

[0121] Secondary Objectives: Sweating episodes, sleep problems, depressed moods, nervousness, urogenital symptoms (vaginal dryness, pollakisuria, nocturia), bleeding patterns. General safety.

[0122] Synopsis: Double-blind, placebo controlled trial with healthy, post-menopausal women randomly assigned to one of 4 groups

[0123] 1 mg E2+1 mg DRSP

[0124] 1 mg E2+2 mg DRSP

[0125] 1 mg E2+3 mg DRSP placebo

[0126] Synopsis:

[0127] Main inclusion criterion: A minimum of 5 moderate to severe hot flashes per day on at least 7 days of the 2-week pre-treatment period.

[0128] The duration of the treatment will be 16 weeks (4-28-day cycles).

[0129] Hot flashes will be assessed by means of recording the frequency and severity (mild, moderate and severe) and comparing these between the verum groups and placebo. The patient will record the incidence and severity of the hot flashes and diary cards. In addition, the investigator will ask the patient at each visit about other typical menopausal symptoms (sweating episodes, sleep problems, depressed moods, nervousness, urogenital symptoms). The intensity of the symptoms will be assessed as mild, moderate or severe.

[0130] If the patient has an intact uterus, the occurrence of bleeding will be recorded every day during the study on diary cards. The patient will make daily entries in the diary card according to the bleeding intensity definitions given below

Code	Category	Definition
0	no	no vaginal bleeding
1	spotting	less than associated with normal menstruation relative to the subject's experience with no need for sanitary protection (except for panty liners)
2	light	less than associated with normal menstruation relative to the subject's experience with no need sanitary protection
3	normal	like normal menstruation relative to the subject's experience
4	heavy	more than normal menstruation relative to the subject's experience

[0131] For urogenital symptoms, the following parameter and categories will be used:

Parameter	Categories
vaginal dryness	yes/no/not applicable
increased frequency of urination	no/yes
nocturia	no/yes ("yes" means at least 2 urinations during 2 or more nights within the preceding week)

[0132] Data Analysis: For the efficacy parameters, both a valid-case analysis (VCA) and an intention to treat (ITT) analysis will be performed. The primary target variable is the individual relative change (C) in the number of hot flashes. C is defined as $(T-B)/B$, where T and B are individual means. T is the mean number of hot flashes per week, calculated by the observations during the weeks 3 through 16 of the treatment phase. B is the mean number of hot flashes per week, calculated from the observations of the 2-week pre-treatment phase.

EXAMPLE 7: Lipid Profile

[0133] Objective: The primary goal of this study is to compare two E2/DRSP treatments and Premique®/Premelle® regarding lipid profile. Lipid profile is generally accepted as the surrogate endpoint to estimate cardiovascular risk.

[0134] Primary Objectives: Lipid pattern including HDL cholesterol, LDL cholesterol

[0135] Secondary Objectives: Lipid pattern including total cholesterol, triglycerides, HDL2 cholesterol, HDL3 cholesterol, VLDL cholesterol, apolipoproteins (A-1, A-2, B, E), Lp(a); Menopausal symptoms; Bleeding pattern; Endometrial safety; General safety

[0136] Design: The study is performed as an open-label, multicentre, comparative study in 300 post-menopausal women randomly assigned to one of 3 groups of 100 after giving their informed consent.

[0137] Groups:

[0138] 1 mg E2+2 mg DRSP

[0139] 1 mg E2+3 mg DRSP Premique®/Premelle® 0.625 mg conjugated estrogens +5 mg MPA

[0140] All treatments are applied daily orally during the whole treatment period of 2 years without a treatment free interval. Measurements of lipid profile are performed at screening and after 12, 28, 52, and 104 weeks of treatment as well as six weeks after treatment.

1. A pharmaceutical composition comprising

as a first active agent, an estrogen (or naturally or synthetic derivative thereof) in sufficient amounts to treat diseases, disorders and symptoms associated with deficient endogenous levels of estrogen in women, and as a second active agent, 6β,7β,15β,16β-dimethylene-3-oxo-17α-preg-4-ene-21,17-carbolactone (drospirenone) in sufficient amounts to protect the endometrium from the adverse effects of estrogen, together with a pharmaceutically acceptable excipient or carrier.

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C.

Abogado
J. Ian Raisbeck

ASUNTO	Radicación	06-110229
	Trámite	011
	Evento	379
	Actuación	430
	Oficio	08531
	Folios	005

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☐ Cap. II ☒
No. Sol. Internacional	<u>PCT/EP2005/002971</u>		
Fecha de Presentación Interna.	<u>19 de marzo de 2005</u>		

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

- | | | | |
|------|--------------------------|--|-------------------------------|
| 1.1. | <u>Descripción:</u> | Folios: 30 a 50 | (como se radicó inicialmente) |
| 1.2. | <u>Reivindicaciones:</u> | Folios: 50 a 53 | (como se radicó inicialmente) |
| 1.3. | <u>Prioridad:</u> | <u>DE 10 2004 016 779.6 de 1 de Abril de 2004</u> | |
| 1.4. | <u>Oposiciones:</u> | Laura Silva por Procaps S.A. (folio 88)
José Reyes por Lafranco S.A. (folio 146) | |

2. Objeto de la invención

- Título de la solicitud: "PREPARACIÓN FARMACÉUTICA PARA APLICAR SOBRE LA PIEL QUE CONTIENE DROSPIRENONA", folio 1, campo 54.
- El objeto de la presente solicitud de patente de invención consiste en:

Reivindicaciones 1-15: Preparaciones farmacéuticas para la piel.

El problema planteado en esta solicitud es la necesidad de formas de administración de gestágenos poco potentes.

Para solucionar este problema técnico la solicitud en estudio proporciona preparaciones farmacéuticas trans-dérmicas de drospirenona.

- La invención se catalogó en la categoría A61K47/32, según la Clasificación Internacional de Patentes (IPC).

3. Análisis de la(s) Oposición(es): (artículo 43 D. 486):

- Se considera relevante el análisis de patentabilidad presentado en las oposiciones, en que se afecta la novedad de la solicitud. El análisis en este concepto técnico se basa en un documento diferente, D1 (US2003144258), y sin embargo llega a conclusión similar.

4. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es la fecha de presentación de la solicitud prioritaria 1 de Abril de 2004.

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación
D1	US2003144258	Drospirenone for hormone replacement therapy	31.07.2003

5. Análisis de patentabilidad (artículo 14 D486)

5.1. Novedad (artículo 16 D486)

- En la primera reivindicación se presentan preparaciones farmacéuticas que contienen drospirenona para aplicación sobre la piel.
- El estado de la técnica representado por D1, presenta composiciones farmacéuticas que contiene drospirenona junto con un vehículo o excipiente farmacéuticamente aceptable para terapia de reemplazo hormonal y puede administrarse como preparación farmacéutica multifase.
- El elemento característico de las composiciones reivindicadas, es decir el contenido de drospirenona, ya era conocido en D1 por lo cual las composiciones no pueden considerarse novedosas.

6. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	US2003144258	1 y dependientes (2 a 15)	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 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 División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha
24 JUL 2009

CONCEPTO TÉCNICO No.2454	EXAMINADOR TÉCNICO Código No.202074
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