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Dados los cuestionamientos realizados a la solicitud en relación con su claridad y la patentabilidad de la materia reivindicada, el solicitante ha decidido eliminar el juego reivindicatorio original (reivindicaciones 1 a 44) y propone las nuevas reivindicaciones anexas con este memorial. En el nuevo capítulo se han eliminado las reivindicaciones dirigidas al método para mejorar la salud de la mujer y las reivindicaciones de uso. Igualmente se han suprimido las palabras subjetivas, como sustancialmente, y el término equipo ha sido reemplazado por kit. En este orden de ideas las nuevas reivindicaciones reclaman el kit tal y como se detalla en el capítulo descriptivo, y lo caracterizan por comprender dos tipos de hormonas sexuales que son presentadas de forma diferente y con rangos de dosificación específicos, con lo cual se superan las objeciones del Examinador.

En relación con la modificación el solicitante desea aclarar que el producto reivindicado es un kit que comprende dos elementos que interactúan más eficientemente cuando son suministrados en las formas y a la específica concentración de hormonas en que la reivindicación lo indica, permitiendo que entre ellos exista una complementariedad que los lleva a actuar como un único producto ideal para aquellas mujeres con niveles elevados de SHBG.

NOVEDAD

Partiendo del principio que cualquier cuestionamiento sobre la novedad requiere que cada uno y todos de los elementos de una reivindicación deben haber sido enseñado o sugerido al menos por una sola referencia de arte previo y basándonos en el nuevo capítulo reivindicatorio resaltamos el hecho que la reivindicación independiente y general 1 caracterizan el kit por comprender un parche transdérmico con andrógeno y una dosis sólida de estrógeno. El parche de andrógeno libera entre 50 a 3000 mcg/día a una usuaria y la dosis de estrógeno sólido contiene 0.2 a 2 mg de estrógeno.

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La cantidad de esteroide androgénico en el medicamento es específicamente seleccionado para ser apropiado para una mujer que tiene niveles elevados o sustancialmente elevados de SHBG y que excede las dosis que son consideradas apropiadas como suplemento de la testosterona femenina tradicional. Las altas dosis de esteroide androgénico pueden inducir un efecto adverso significativo en la salud de una mujer con niveles normales de SHBG. Con lo cual, para mujeres con niveles elevados o sustancialmente elevados de SHBG, esta invención proporciona niveles funcionales de biodisponibilidad de andrógeno en el suero los cuales son terapéuticos para la mujer y no le causan daño o efectos colaterales adversos, a pesar del hecho de que los niveles de andrógeno total alcanzados son suprafisiológicos y pueden ser dañinos para una mujer con niveles normales de SHBG.

Ahora bien, comparando las referencias citadas por el Examinador y la invención reclamada en las nuevas reivindicaciones se observa que en el estado del arte no se había divulgado la forma de combinación de dosis proporcionada por la presente invención.

El Examinador ha establecido que las referencias D1 a D4 afectan la novedad de la presente invención porque cada una también muestra métodos no orales de administración de esteroides androgénicos. D1 muestra la administración a una mujer (que requiere una terapia de reemplazo de hormonas) de un parche de testosterona y opcionalmente de un estrógeno. D2 muestra la administración del precursor de esteroide sexual deshidroepiandrosterona (DHEA) por medio de varios métodos percutáneos o de liberación transmucósica. D3 muestra una crema aplicada tópicamente para liberar testosterona, estrógeno, y progestina a mujeres postmenopáusicas. D4 también muestra una crema aplicada tópicamente que contiene DHEA, y opcionalmente estradiol.

Diferente de dicha información y contrario a lo que al parecer entiende el examinador, la presente invención tal como se establece en las nuevas reivindicaciones 1 a 12, no se dirige a un parche de administración no oral de un andrógeno, la invención

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reivindicada se refiere al kit que comprende el parche de administración no oral de un andrógeno en combinación con una forma de administración oral de un estrógeno. Lo cual no es ni planteado ni enseñado por ninguna de las referencias citadas.

Mientras que D1, D3 y D4 divulgan la administración de ambas hormonas andrógeno y estrógeno en combinación, cada una muestra la administración transdérmica o transmucósica. D2 también muestra la administración de estrógenos, pero solamente en la misma forma de dosificación como DHEA (también preferentemente transdérmica). Ver columna 18, líneas 45 a 49. Por lo tanto, el solicitante establece que la invención reclamada en las presentes reivindicaciones es novedosa ante las referencias D1-D4 toda vez que ellas no muestran un producto que comprenda una forma farmacéutica de estrógeno para administración vía oral junto con una forma farmacéutica de andrógeno para administración no oral.

Adicional a lo expuesto, las referencias citadas por el Examinador no muestran las concentraciones apropiadas para mujeres con elevado SHBG, las cuales son reivindicadas en el capítulo reivindicatorio y constituyen parte esencial de la invención pues sin dichas dosis y las dos formas farmacéuticas distintas, es decir oral y no oral, el kit no lograría el efecto que actualmente presenta y que le permite ser un producto farmacéutico ideal para el tratamiento de mujeres con un elevado nivel de SHBG.

Complementando lo expuesto, la invención de la presente invención es novedosa ante D1-D4 ya que ninguna de las referencias citadas por el Examinador muestra dosis de hormonas apropiadas para mujeres que tienen niveles elevados o sustancialmente elevados de SHBG. D1 se refiere a la restauración de los niveles de testosterona en una mujer a un nivel que corresponde sustancialmente a niveles endógenos en sangre de testosterona en mujeres jóvenes adultas sanas ("corresponds substantially to endogenous blood levels of testosterone in healthy young adult women"). Ver página 3, líneas 28 a 35; página 4, líneas 15 a 18; página 5, líneas 32 a 35.

De igual manera, D2 concierne principalmente a la administración de precursores de

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esteroides sexuales a manera de recuperar o mantener los niveles del esteroide deseado que son considerados como "normales" para un hombre joven sano, o para una mujer antes de la menopausia. Ver columna 19, líneas 19 a 29.

La referencia D3 proporciona una terapia tópica de reemplazo de hormonas que incluye hormonas "naturales" (por ejemplo hormonas derivadas de una fuente natural). En las referencias D1 y D2, las formulaciones son utilizadas como terapias de reemplazo para restablecer los niveles de hormonas en suero humano a valores encontrados en la fase luteínica temprana en una mujer ovulante premenopáusica ("restore human serum levels of these hormones to values found in early luteal phase in premenopausal ovulatory women"). Ver página 7, líneas 4 a 8. D4 no muestra niveles particulares de testosterona. La invención en D4 se dirige hacia el reemplazo de niveles fisiológicos ("replacing the physiological levels") en varias etapas de la vida. Ver página 2, líneas 33 y 34.

Las referencias D1 a D4 se dirigen cada una hacia alcanzar los niveles "normal"/"fisiológico" de andrógeno en suero. Por el contrario, la presente invención se refiere a dirigir a los síntomas de los bajos niveles de andrógeno en la sangre en mujeres con niveles elevados de SHBG. Estas mujeres necesitan por lo tanto alcanzar niveles totales de testosterona en suero mucho más altos que los de las mujeres normales para tener un nivel similar de testosterona disponible. De acuerdo con esto, la presente invención muestra la administración suficiente de hormona para alcanzar niveles suprafisiológicos totales de testosterona en suero.

Alcanzar los "niveles normales" a los cuales D1 a D4 están dirigidos sería insuficiente para proporcionar un efecto terapéutico cuando el nivel de SHBG es elevado. Nada en ninguna de las referencias citadas por el Examinador muestra o sugiere que la testosterona debe ser administrada en una cantidad que proporcione niveles suficientes para tener un efecto positivo en vista de niveles elevados o sustancialmente elevados de SHBG, o que los niveles endógenos que se busca obtener serían funcionalmente deficientes cuando SHBG es elevado o sustancialmente elevado. El solicitante sostiene que la presente invención es nueva ante D1 a D4 porque no se

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manifiesta en ninguna de las referencias las dosis de testosterona suficientes para tener un efecto terapéutico en mujeres con niveles elevados o sustancialmente elevados de SHBG.

Como se concluye de los argumentos expuestos, las referencias citadas por el Examinador no muestran los elementos de la presente invención. Por consiguiente, es posible afirmar que la invención reivindicada es nueva y por ende, cumple con el requisito de novedad exigido por el artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina.

Por lo tanto, se solicita respetuosamente a la Oficina de Patentes Colombiana retirar todas las objeciones.

Agradezco continuar con el presente trámite.

Señor Jefe,



DILIA RODRIGUEZ D'ALEMAN

MRO/srch

FORMULARIO ÚNICO DE CORRECCIONES Y MODIFICACIONES
2000-10

1) SOLICITUD DE:

☐ Corrección de error material

☒ Modificación a una solicitud

2) SOLICITANTE

Nombre: **WATSON**
PHARMACEUTICALS, INC.

Dirección: 311 Bonnie Circle, Corona,
California 91718 Estados Unidos

Nacionalidad o Domicilio: Corona,
California, Estados Unidos

Lugar de Constitución: California,
Estados Unidos

Teléfono: . Fax:
E. Mail:

IDENTIFICACIÓN

C.C. ☐ NIT: ☐

C.E. ☐ OTRO ☐

NÚMERO

**3) REPRESENTANTE
O APODERADO**

Nombre: **DILIA MARÍA**
RODRÍGUEZ D'ALEMAN

Dirección: Carrera 11 N°. 86-53
Piso 6 Bogotá D.C.

Teléfono: 6181088 Fax: 6350824
E. Mail: info@clarkemodet.com.co

IDENTIFICACIÓN

C.C. ☒ NIT: ☐

C.E. ☐ OTRO ☐

NÚMERO: 41.654.882
TP: 20824 CSJ

4) NUMERO DE EXPEDIENTE: 00043097

5) DESCRIPCIÓN DE LA CORRECCIÓN O MODIFICACIÓN SOLICITADA:

Se presente nuevo capítulo reivindicatorio y título.

6) Comprobante de pago No. 05-49,298 Fecha: Julio 1, 2005

7) Anexos:

☒ Comprobante de la tasa

☐ Poderes, si fuere el caso

☐ Certificado de Existencia y Representación legal, cuando el solicitante sea persona Jurídica

8)

Nombre: **DILIA RODRÍGUEZ D'ALEMAN** Firma: 

C.C.: 41.654.882 TP: 20824 CSJ

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 05 - 49,298
FECHA : JULIO 1 DE 2005

SUPERINDUSTRIA Y COMERCIO
Radicacon : 00043097 00000006
Fecha (AMD): 2005-07-27 16:38:35
Tramite : 002 PATENTES D 1 REGISTRO/ 444 REPUESTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Folios: 12

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PAGO	Vr. PAGO
CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO POPULAR	050-00110-6	35424585	01/07/2005	6.856.000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	
		12 MARCAS Y LENAS COMERCIALES	91.000.00
		TOTAL :	\$ 91.000.00

SON: NOVENTA Y UNO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

315 321 6 9

REIVINDICACIONES

1. Un kit de hormonas sexuales para mejorar la salud de una mujer que tiene un elevado
5 o sustancialmente elevado nivel de hormonas sexuales que enlazan globulina (SHBG), caracterizado porque comprende: un parche transdérmico de andrógeno que libera de 50 a 3000 mcg/día de andrógeno; y al menos un estrógeno, en
10 una forma de dosificación oral que contiene de 0.2 a 3 mg del estrógeno.

2. Un kit de hormonas sexuales según la reivindicación 1, caracterizado porque el parche transdérmico de testosterona es un parche de
15 matriz.

3. Un kit de hormonas sexuales según la reivindicación 1, caracterizado porque el parche transdérmico de testosterona es un parche de depósito.

20 4. Un kit de hormonas sexuales según la reivindicación 1, caracterizado porque el andrógeno es un elemento seleccionado del grupo que consiste de: testosterona, metiltestosterona, androstenediona, adrenosterona,
25 deshidroepiandrosterona, oximetolona,

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fluoximesterona, metandrostenolona, testolactona,
pregnolona, 17 α -metilnortestosterona,
noretandrolona, deshidrotestosterona, danazol,
oximetolona, androsterona, nandrolona,
5 estanozolol, etilestrenol, oxandrolona,
bolasterona y mesterolona, propionato de
testosterona, cipionato de testosterona,
fenilacetato de testosterona, enantato de
testosterona, acetato de testosterona, buciclato
10 de testosterona, heptanoato de testosterona,
decanoato de testosterona, caprato de
testosterona, isocaprato de testosterona, isómeros
y derivados de los mismos, y una combinación de
los mismos.

15 5. Un kit de hormonas sexuales según la
reivindicación 4, caracterizado porque el
andrógeno es testosterona.

6. Un kit de hormonas sexuales según la
reivindicación 1, caracterizado porque el
20 estrógeno es un elemento seleccionado del grupo
que consiste de: 17 α -estradiol, 17 β -estradiol,
estrógeno conjugado equino, estrógeno
esterificado, estradiol micronizado, sulfato de
estrógeno sódico, etinil estradiol, estrona,
25 modulador receptor de estrógeno selectivo (SERM),

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fitoestrógeno, isómeros y derivados de los mismos y una combinación de los mismos.

7. Un kit de hormonas sexuales según la reivindicación 6, caracterizado porque el estrógeno es un elemento seleccionado del grupo que consiste de: 17α -estradiol, 17β -estradiol, estrógeno conjugado equino

8. Un kit de hormonas sexuales según la reivindicación 1, caracterizado además porque comprende una tableta de progestina que contiene 5mg de una progestina seleccionada del grupo que consiste de progesterona, acetato de medroxiprogesterona, noretindrona, acetato de noretindrona, isómeros y derivados del mismo y una combinación de los mismos.

9. Un kit de hormonas sexuales según la reivindicación 8, caracterizado porque la progestina es progesterona.

10. Un kit de hormonas sexuales según la reivindicación 6, caracterizado porque el estrógeno esterificado se selecciona del grupo que consiste de estradiol-3,17-diacetato, estradiol-3-acetato, estradiol-17-acetato, estradiol-3,17-divalerato, estradiol-3-valerato y estradiol-17-valerato.

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11. Un kit según la reivindicación 6, caracterizado porque el modulador receptor de estrógeno selectivo es raloxifeno.

12. Un kit de hormonas sexuales según la 5 reivindicación 6, caracterizado porque el fitoestrógeno se selecciona del grupo que consiste de genisteína, diadzeína y ecuol.

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

2020
Bogotá, D.C.,

Doctora
DILIA RODRÍGUEZ D'ALEMÁN
(Apoderado)

ASUNTO	Radicación	00043097
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	
	Folios	016

7083

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:

Documentos estudiados:

Los textos estudiados fueron la descripción (Folios: 4 a 49) y las reivindicaciones modificadas 1 a 12 (Folios: 321 a 324).

La presente solicitud reivindica prioridad americana N° US60.138851 de 11 de junio de 1999 y cumple con lo establecido en los artículos 9, 10 y 11 de la Decisión 486 de la Comisión de la Comunidad Andina.

Objeto de invención:

La presente solicitud se titula: "Equipo para administración de hormonas sexuales".

El objeto de la presente solicitud se refiere a la administración de andrógenos a mujeres. Por lo tanto, la presente solicitud cubre los campos de las ciencias farmacéuticas y medicina (ver folio: 4).

Según la descripción, se sabe que un nivel funcional de hormonas androgénicas promueven la salud y actividad sexual, la sensación de bienestar, maximizan la masa y función muscular e inhiben el desgaste del sistema óseo en las mujeres. Además, un nivel funcional de hormonas androgénicas pueden promover la salud cardiovascular y coronaria, disminuyen la sensibilidad del pecho, disminuyen la inestabilidad vasomotora, modulan la función inmunológica, aumentan ciertas habilidades cognoscitivas, mejoran la salud urogenital, reducen los efectos colaterales relacionados con la suplantación de estrógenos y proporcionan efectos neuroprotectores directos.

De acuerdo con la presente solicitud, el uso de estrógenos orales eleva los niveles de suero SHBG. Los niveles de SHBG también son elevados en varias condiciones, por ejemplo, hipertiroidismo y embarazo y por algunos otros medicamentos, por ejemplo, anticonvulsivos. Los niveles elevados de SHBG, alteran los niveles de hormonas androgénicas y las dosis necesarias para alcanzar niveles funcionales. La

presente solicitud proporciona métodos, composiciones y equipos para alcanzar niveles funcionales de esteroides androgénicos en mujeres, con niveles elevados de SHBG y de este modo, mejorar su salud.

Lo que se reivindica como novedoso es lo siguiente:

Un kit de hormonas sexuales para mejorar la salud de una mujer que tiene un elevado o sustancialmente elevado nivel de hormonas sexuales que enlazan globulina (SHBG), caracterizado porque comprende: un parche transdérmico de andrógeno que libera de 50 a 3000 mcg/día de andrógeno; y al menos un estrógeno, en una forma de dosificación oral que contiene de 0.2 a 3 mg del estrógeno.

El objeto de la solicitud definido anteriormente se clasificó en la IPC A61K 31/56, 31/705.

Claridad de la solicitud:

El artículo 30 de la Decisión 486 de la Comisión de la Comunidad Andina establece que: "Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción."

Las reivindicaciones podrán ser independientes o dependientes. Una reivindicación será independiente cuando defina la materia que se desea proteger sin referencia a otra reivindicación anterior. Una reivindicación será dependiente cuando defina la materia que se desea proteger refiriéndose a una reivindicación anterior. Una reivindicación que se refiera a dos o más reivindicaciones anteriores se considerará una reivindicación dependiente múltiple."

De acuerdo con lo anterior, el título no corresponde con lo que se está reivindicando puesto que las reivindicaciones se refieren a un "kit" y el título a un "equipo".

Excepciones de Patentabilidad:

El artículo 20 de la Decisión 486 se establece: "No serán patentables: a) las invenciones cuya explotación comercial en el territorio del País Miembro respectivo deba impedirse necesariamente para proteger el orden público o la moral. A estos efectos la explotación comercial de una invención no se considerará contraria al orden público o a la moral solo debido a la existencia de una disposición legal o administrativa que prohíba o que regule dicha explotación; b) las invenciones cuya explotación comercial en el País Miembro respectivo deba impedirse necesariamente para proteger la salud o la vida de las personas o de los animales, o para preservar los vegetales o el medio ambiente. A estos efectos la explotación comercial de una invención no se considerará contraria a la salud o la vida de las personas, de los animales, o para la preservación de los vegetales o del medio ambiente sólo por razón de existir una disposición legal o administrativa que prohíba o que regule dicha explotación; c) las plantas, los animales y los procedimientos esencialmente biológicos para la producción de plantas o animales que no sean procedimientos no biológicos o microbiológicos; d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales."

De acuerdo con lo anterior, la(s) reivindicación(es): 1 a 12 (Folios: 321 a 324), que, si bien se refieren a un kit de hormonas sexuales,... caracterizado porque comprende un parche transdérmico de andrógeno,... y al menos un estrógeno,... en una forma de dosificación oral, no es patentable por cuanto en realidad se relaciona con un método de administración de un andrógeno y un estrógeno. Esto se puede corroborar en las dos solicitudes de prioridad en las cuales se reivindica un método de tratamiento donde se administran un andrógeno y un estrógeno.

Determinación del estado de la técnica:

El artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral,

utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de Patente o, en su caso, de la prioridad reconocida.

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

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 11/06/1999, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

Se hizo la búsqueda de documentos relevantes en el estado de la técnica, entendiendo como estado de la técnica la definición provista en el artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina y las excepciones fijadas en el artículo 17 de la misma.

Se encontró como anterioridades (documentos cuya fecha de publicación es anterior a la fecha de presentación de la primera solicitud de patente sobre la cual se reivindica prioridad o de la fecha de presentación de esta solicitud) que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de Publicación
1	WO 95/03764	Skin patches and methods for providing testosterone	9 de febrero de 1995
2	US 5872114	Therapeutic methods and delivery systems utilizing sex steroid precursors	16 de febrero de 1999
3	WO 98/02167	Transdermal application of naturally occurring steroid hormones	27 de enero de 1998
4	US 5468736	Hormone replacement therapy	21 de noviembre de 1995
5	US 5770226	Combined pharmaceutical estrogen-androgen-progestin oral contraceptive	23 de junio de 1998
6	US 5827843	Preparation for substitution therapy, containing at least one progestogen and at least one estrogen	27 de octubre de 1998

Evaluación de los requisitos de Patentabilidad:

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

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

Evaluación de Nivel Inventivo:

El artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica".

El Nivel Inventivo se evaluó por comparación entre lo solicitado y encontrado en el estado de la técnica y que se relaciona con el objeto reivindicado y de acuerdo con la definición de nivel inventivo del Artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina.

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

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

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

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

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

El documento **US 5468736** (folios: 330 a 334) menciona una terapia de reemplazo hormonal donde se administra estrógeno vía oral.

El documento **US 5770226** (folios: 335 y 336) menciona preparaciones orales que contienen estrógeno, progestina y/o un andrógeno y métodos para administrarlos.

El documento **US 5827843** (folios: 337 a 340) menciona una preparación para terapia de sustitución que está compuesta por un progestágeno y un estrógeno los cuales pueden administrarse en forma separada para la misma terapia; el progestágeno puede aplicarse mediante implante (parche) y el estrógeno en forma oral.

Analizando estos documentos se encuentra claramente que ya era conocida la administración de andrógenos vía transdérmica, por ejemplo, con un parche; además ya se conocían preparaciones orales con estrógenos y que pueden administrarse indistintamente junto con un progestágeno o con un andrógeno; igualmente, ya era conocida la administración de estrógeno en forma oral y un progestágeno en forma de parche para el mismo tratamiento.

Aunque el progestágeno es distinto a un andrógeno, de todas formas ya se había establecido la forma de administración de que trata la presente solicitud, es decir, dos tipos de hormonas administradas en formas distintas y por separado

(transdérmica y oral). La respuesta al problema técnico que se pretendía resolver, resulta obvia partiendo de las anterioridades en mención.

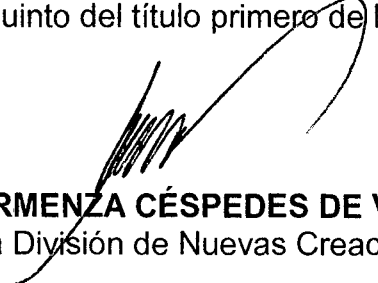
Como se observa, el objeto de esta solicitud podría resultar obvio para una persona del oficio normalmente versada en la materia y derivarse de manera evidente del estado de la técnica.

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

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	WO 95/03764	1 a 12	Nivel Inventivo
2	US 5872114	1 a 12	Nivel Inventivo
3	WO 98/02167	1 a 12	Nivel Inventivo
4	US 5468736	1 a 12	Nivel Inventivo
5	US 5770226	1 a 12	Nivel Inventivo
6	US 5827843	1 a 12	Nivel Inventivo

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL

Jefe de la División de Nuevas Creaciones

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

17⁸ AGO. 2005

CONCEPTO TÉCNICO Nº: 1170	EXAMINADOR TÉCNICO Código Nº: 202005	EXAMINADOR JURÍDICO Código Nº:
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[54] HORMONE REPLACEMENT THERAPY

[75] Inventor: Gary D. Hodgen, Norfolk, Va.

[73] Assignee: The Medical College of Hampton Road, Norfolk, Va.

[21] Appl. No.: 23,692

[22] Filed: Feb. 25, 1993

[51] Int. Cl.⁶ A61K 31/56

[52] U.S. Cl. 514/179; 514/170

[58] Field of Search 514/170, 179

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Primary Examiner—Kimberly R. Jordan

Attorney, Agent, or Firm—Ostrolenk, Faber, Gerb & Soffen

[57]

ABSTRACT

A method of hormone replacement therapy involves the administration of estrogen together with an amount of antiprogesterin which inhibits estrogen-induced endometrial proliferation in a woman.

20 Claims, 1 Drawing Sheet

HORMONE REPLACEMENT THERAPY

BACKGROUND OF THE INVENTION

More than 40 million women in the United States alone have entered their post-menopausal years. The life expectancy of a woman who has attained her last menstrual period is about 28 years and a study in 1982 indicated that about 75 to 85% of these women will develop symptoms of estrogen deficiency (Hammond et al., *Fertilo Steril.* 37(1): 5-25, 1982). One of the most common complaints of women following the commencement of ovarian failure is the "hot flash" or vasomotor symptom complex. This is characterized by a sudden onset of warmth generally lasting a few minutes, frequently evidenced by a visible red flush, and often accompanied by dizziness, nausea, headache, palpitations and diaphoresis. Adequate estrogen supplementation has been shown to provide relief to over 90% of these individuals.

There are many other post-menopausal symptoms of chronic hypoestrogenism, among the most serious is osteoporosis and ischemic heart disease. As many as 25% of women over 60 years old have documented spinal compression fractures as a result of osteoporosis related to estrogen deficiency and as many as 50% develop vertebral fractures by age 75°. A very large percentage of hip fractures in the elderly are attributable to osteoporosis. In 1980, a study carried out at the Mayo Clinic calculated the cost of hospital stays due to fractures at over one billion dollars per year (Gallagher et al., *Clin. Ortho.*, 150:163, 1980).

Long-term estrogen replacement therapy is common for post-menopausal and other estrogen deficient women. It is, however, a more complicated issue for women having a uterus. Estrogen therapy has been associated with an increased incidence of endometrial cancer due to the continual "unopposed" estrogen-induced proliferation of the endometrium. Regular progestin administration inhibits the continual estrogen stimulation of the endometrium through an anti-proliferative effect and seems to reduce the rate of endometrial carcinoma in post-menopausal women receiving estrogen by several fold (Barbieri et al., *Menopause Management*, July/August 1992, 12-24). However, combination of estrogen and progestin frequently causes undesirable uterine bleeding which reduces the rate of patient compliance. There is also concern that the cardiovascular benefits of estrogen might be minimized by progestins (Speroff, *Current Trends in Estrogen Replacement Therapy*, 1986). Nevertheless, both sequential and concurrent estrogen plus progestin regimens are now predominately used in hormone replacement therapy for menopausal women with a uterus. Notwithstanding the above, a woman without a uterus is adequately treated by estrogen alone.

Despite the well-established overall benefits of estrogen plus progestin replacement therapy for women having a uterus, the rate of patient compliance with this therapy suffers markedly because the treatment often requires women to endure side effects such as unpredictable bleeding and cyclotherapeutic withdrawal menstrual bleeding during a time in their lives when many women welcome cessation of menstrual bleeding as a normal occurrence in menopause. These side effects can be experienced during the entire treatment interval, which could be for the remainder of life. User satisfaction and compliance should all increase greatly if the principal benefits of the estrogen replacement therapy could be maintained while the estrogen-induced endometrial proliferation is inhibited without uterine bleeding.

The nature of the invention described here stems from the antiproliferative action of antiprogesterin, i.e., its ability to inhibit endometrial proliferation during hormonal replacement therapy. This antiproliferative effect by antiprogesterins per se has been noted (Gravanis et al., *J Clin Endocrinol Metab.* 60: 156, 1986; Wolf et al., *Fertil Steril.* 52:1055, 1989; Chualisz et al., *Endocrinology*, 129: 312, 1991), but the therapeutic value of this effect for hormone replacement therapy to menopausal women (which extends over a minimum interval of 20 days) has not been previously recognized.

The absence of thickening (proliferating) endometrium, as can be achieved with the administration of antiprogesterins during extended estrogen replacement therapy, would decrease the risk of endometrial carcinoma (which is also decreased with progestins), but unlike that obtained with progestins would avoid unwanted vaginal bleeding that markedly reduces therapy compliance among postmenopausal women. Moreover, the addition of estrogen in combination with antiprogesterin provides this advantage without negating the bone conserving efficacy derived from estrogen replacement therapy. These therapeutic advantages are achieved without any complications that accompany progestin administrations which in this invention is excluded in its entirety.

It is accordingly the object of this invention to provide a method of inhibiting the estrogen-induced proliferation of the endometrium without undesirable uterine bleeding and without sacrificing the advantageous properties of estrogen replacement therapy. This and other objects of the invention will become apparent to those of ordinary skill in the art from the following detailed description.

SUMMARY OF THE INVENTION

This invention broadly relates to a method of hormone replacement therapy. More particularly, it relates to a method of hormone replacement therapy in which an estrogen replacement therapy effective amount of estrogen is administered to women in need of such therapy and, in addition, antiprogesterin is also administered in an amount which inhibits estrogen-induced endometrial proliferation, thus avoiding uterine bleeding.

BRIEF DESCRIPTION OF THE DRAWING

The FIGURE shows the dependency of the urinary calcium/creatinine ratio on estrogen.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, a hormone replacement therapy is provided employing an estrogen together with the co-administration of an amount of antiprogesterin which inhibits estrogen-induced endometrial proliferation.

The estrogen aspect of the invention is analogous to conventional estrogen replacement therapy. Accordingly, any known estrogen material, dosage amount and method heretofore employed in the usual estrogen replacement therapy can be employed in the practice of the present invention. Examples of estrogens which can be employed are ethinyl estradiol and estradiol and their esters such as the acetate, valerate or benzoate, mestranol and conjugated equine estrogens. The estrogen is administered in the conventional manner by any route where it is active, for instance

orally or transdermally. Most estrogens are orally active and that route of administration is therefore preferred. Accordingly, administration forms can be tablets, dragees, capsules or pills which contain the estrogen and a suitable pharmaceutically acceptable carrier.

For example, the amount of conjugated equine estrogen administered is analogous to that practiced in conventional estrogen replacement therapy and is generally in the range of about 0.3 to 1.2 mg, preferably about 0.625 to 0.9 mg daily. The determination of an effective dose is a routine exercise in the pharmaceutical arts, taking into account such various physical parameters as weight, age and the like, and is best determined by the attending clinician. The administration can be periodic, such as on a weekly basis, or continuous such as on a daily basis. The latter, that is daily administration, is preferred because individuals are more likely to follow the treatment regimen and not to forget or overlook a periodic administration schedule.

The antiprogesterin can be a progesterone receptor antagonist or a pharmaceutically suitable agent that counteracts the normal biological activity of progesterone. A preferred antiprogesterin is a progesterone receptor antagonist. For example, RU 486 is particularly suitable in the practice of this invention.

Examples of antiprogesterins which can be employed in this invention are RU 486 ("mifepristone", Roussel Uclaf, Paris; U.S. Pat. No. 4,386,085); and "onapristone" (Schering Ag, Berlin; U.S. Pat. No. 4,780,461) and the steroids described in the following patents and patent applications; U.S. Pat. No. 4,609,651, especially the compound lilepristone (11 β -(4-dimethylaminophenyl)-17 β -hydroxy-17 α -(3-hydroxyprop-1-(Z)-enyl)-4,9(10) estradien-3-one); U.S. application Ser. No. 06/827,050, especially the compounds acetylphenyl-17 β -hydroxy-17 α -(1-propinyl)-4,9-estradien-3-one and 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(3-hydroxy-1(2)-propenyl)-4,9-estradien-3-one; U.S. application Ser. No. 07/283,632; published European patent application EP-A 04042831; and other anti-progesterins, e.g., U.S. Pat. No. 4,891,368.

The antiprogesterin can be administered by way of any art recognized means as practiced in the pharmaceutical arts. For example, a suitable antiprogesterin may be so formulated so that it can be administered orally, via a skin patch for transdermal absorption, contained within an inert matrix which is implanted within the body and in the depot state or intravaginally in a matrix that slowly releases the antiprogesterin (such an implant is taught in U.S. Pat. Nos. 4,957,119 and 5,088,505 and the like).

Pharmaceutical formulations containing the antiprogesterin and a suitable carrier can be solid dosage forms which includes tablets, capsules, cachets, pellets, pills, powders or granules; topical dosage forms which includes solutions, powders, fluid emulsions, fluid suspensions, semi-solids, ointments, pastes, creams, gels or jellies and foams; and parenteral dosage forms which includes solutions, suspensions, emulsions or dry powder comprising an effective amount of antiprogesterin as taught in this invention. It is known in the art that the active ingredient, the antiprogesterin, can be contained in such formulations in addition to pharmaceutically acceptable diluents, fillers, disintegrants, binders, lubricants, surfactants, hydrophobic vehicles, water soluble vehicles, emulsifiers, buffers, humectants, moisturizers, solubilizers, preservatives and the like. The means and methods for administration are known in the art and an artisan can refer to various pharmacologic references for guidance. For example, "Modern Pharmaceutics", Banker &

Rhodes, Marcel Dekker, Inc. 1979; "Goodman & Gilman's The Pharmaceutical Basis of Therapeutics", 6th Edition, MacMillan Publishing Co., New York 1980 can be consulted.

The estrogen and antiprogesterin components of the hormone replacement therapy methods of the invention can be co-administered utilizing the same or different dosage forms or means, for example the same tablet, or the estrogen component may be provided continuously by implant or depot with supplemental amounts of antiprogesterin provided orally on a periodic basis. Application of the components, compositions and methods of the present invention for the medical or pharmaceutical uses described herein can thus be accomplished by any clinical, medical or pharmaceutical methods and techniques as are presently or prospectively known to those skilled in the art.

The pharmaceutical formulations may be provided in kit form containing a plurality of, generally at least about 20, and preferably in multiples of 7 such as 28, tablets, intended for ingestion on successive days. Where administration of the antiprogesterin is intended to be periodic, a plurality, generally at least three, of non-adjacent tablets contain the antiprogesterin while the remaining tablets are placebo. Where convenient, the kit may provide the estrogen and antiprogesterin can be in the same tablet.

The administration of the antiprogesterin is in an amount which inhibits estrogenic endometrial proliferation. This is generally about 0.005 to 1 mg/kg, and preferably about 0.05 to 0.5 mg/kg, daily in the case of RU 486. Other milligram amounts may be appropriate in the case of different antiprogesterins. Regimens of estrogen and antiprogesterin other than daily and/or in which the dosage amount of the estrogen and antiprogesterin is periodically varied are also within the scope of the invention. It should also be appreciated that a minor amount of periodic bleeding or spotting on a monthly or yearly basis can occur. In other words, the amenorrhea state (the absence of menstrual-like bleeding) established in this invention is substantially, but not necessarily totally, complete. The appropriate amount of the antiprogesterin in the practice of the present invention can, as with the estrogen amount, be determined by using art recognized methods, for example by establishing dose-response curves in suitable primate models and extrapolating to humans, extrapolating from suitable in vitro systems or determining effectiveness in clinical trials. The attending clinician will, as in the case of the estrogen, take weight, age and other physical and medical parameters into account when establishing an appropriate dosage amount.

The administration of the antiprogesterin can either be periodic such as on a weekly basis or continuous, that is on a daily basis. A daily administration is preferred because individuals are more likely to follow the treatment regimen and not to forget or overlook a periodic administration schedule. In the case of the antiprogesterin RU 486, a suitable human oral dose will be on the order of about 0.5 to 10 mg per dose, preferably about 1 to 5 mg per dose daily. This amount can be lowered or raised based on the administration regimen and based on the characteristics of the individual receiving the treatment. Variations of dosage based on the route of administration may vary and such changes can be determined practicing known techniques.

In order to further illustrate the present invention, specific examples are set forth below. It will be appreciated, however, that these examples are illustrative only and are not intended to limit the scope of the invention.

EXAMPLE 1

For the purposes of this study, the antiprogesterin selected was RU 486 and this was administered to female monkeys,

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which are recognized to be a suitable model for human research.

Thirty adult female cynomolgus monkeys (*Macaca fascicularis*) weighing 3.1 to 5.2 kg and having presumably ovulatory, regular menstrual cycles were housed in individual cages which had food and water available at libitum, except when urine was collected. These collections were made after overnight fasting with provision of distilled drinking water in order to avoid contamination with food and/or fecal matter. Detection of blood in the vagina was accomplished by daily vaginal swabs between 6 and 9 A.M. using a saline moistened cotton-tipped applicator. Blood and urine specimens were obtained at the commencement of the study, 10 days after surgical bilateral ovariectomy, 30 days after initiation of treatment, 60 days after initiation of treatment and 90 days after initiation of treatment.

The monkeys were randomly assigned to four groups. Five monkeys were in group I and these constituted ovariectomized controls. Group II consisted of fifteen monkeys which were treated with 0.15 mg conjugated equine estrogens (hereinafter CEE) orally per day. Group II was subdivided into three groups of five animals each, and the subgroups were treated for 30; 60 or 90 days, respectively. Group III consisted of five monkeys which were treated with 0.15 mg CEE orally per day and also administered 0.5 mg of the antiprogesterin RU 486 orally per day for 90 days. Group IV consisted of five monkeys which were treated in the same way as Group III except that the dosage of RU 486 was 10 mg. All medications were administered by gavage between 6 and 9 A.M.

Table 1 below summarizes the incidents of bleeding, either withdrawal menses or breakthrough bleeding, among the treatment groups.

inconsequential in all groups. The additional administration of the antiprogesterin at both dosages markedly curtailed bleeding of any kind and except for a few episodes of spottings a state approaching amenorrhea was sustained in the two weeks after the treatment ended. This was particularly evident at the higher dosage level. The lack of withdrawal bleeding was statistically significantly different.

The data set forth in the FIGURE demonstrates the acute dependency of the urinary calcium/creatinine ratio on an adequate physiologic supply of estrogen. The CEE dosage employed was fully sufficient to restore this metabolic marker to near pretreatment levels at 30, 60 and 90 days. Importantly, addition of the antiprogesterin to achieve an atrophic endometrial status and amenorrhea did not deter the acute beneficial effects of the estrogen therapy. A consistent trend, albeit not statistically significant, shows the RU 486 may have lowered the calcium/creatinine ratio even more than CEE alone.

The data obtained during the study confirms that the antiprogesterin used in the combination with the estrogen in the hormone replacement therapy regimen was highly advantageous. It showed an avoidance of menses induced by cyclic therapeutic regimens, without sacrificing the protective actions of estrogen therapy on acute calcium homeostasis as assessed by urinary excretion. In like manners these data suggest that benefit of estrogen can be retained within the range of antiprogesterin dosage which attains amenorrhea without compromising the beneficial effects of estrogen on proliferative actions of the body, including: coronary vessels, vaginal tissues, temperature regulation of the hypothalamus, dermatological effects, mood effects and the like. The antiprogesterin may counter the known association between estrogen therapy and breast cancer risk in that the administration of the antiprogesterin may counteract estrogen-depen-

Endometrial Status During Conjugated Equine Estrogen Treatment, with and Without Antiprogesterin Therapy in Ovarian Primates¹: Withdrawal Menses and Breakthrough Bleeding As An Indication of Proliferative Versus Atrophic Tissue

Monkey Groups	N	Treatment Interval (Days)	Incidents of Breakthrough Bleeding ⁴ (Days)	Withdrawal Menses ⁴ Range of		Duration of Withdrawal Bleeding ⁴ Days; x + SEM
				Individuals	Days Detected	
I. Untreated Controls	5	—	0	0/5	—	—
II. CEE ²	5	30	0	5/5	32 to 44	5.2 ± 4.4
0.15 mg	5	60	3	5/5	63 to 71	6.6 ± 3.7
Alone	5	90	2	5/5	92 to 103	6.4 ± 4.5
III. CEE ²	5	90	0	3/5	one day 94 and 96 one day 93 only one day 96 only	<1 ⁵
0.15 mg + AP ³						
5.0 mg						
IV. CEE ²	5	90	2	1/5	day 95 only	<1 ⁵
0.15 mg + AP ³						
10.0 mg						

¹Cynomolgus monkeys were ovariectomized 10 days before initiation of treatments.

²Conjugated equine estrogens (CEE), orally administered daily

³Antiprogesterin (AP), RU486 orally administered daily.

⁴Blood in the vagina was detected by daily swabs.

⁵Significantly reduced withdrawal bleeding (P < 0.005)

The administration of the estrogen alone uniformly led to withdrawal bleeding regardless of the length of the treatment and the duration of the bleeding was highly individualized, averaging from 5 to 6 days, although the onset and cessation were spread over almost two weeks after ending the CEE administration. Breakthrough bleeding was negligible and

dant tumor growth and/or progestin-dependant tumor growth.

EXAMPLES 2-9

Following the procedures set forth in Example 1, hormone replacement study is repeated with the following

combination of agents:

Example	Estrogen	Antiprogesterin
2	estriol (E3)	onapristone
3	estetrol (E4)	lilopristone
4	estradiol	11 β -(4-acetyl-phenyl)-17 β -hydroxy-17 α -(1-propinyl)-4,9-estradien-3-one
5	estrone	11 β -(4-acetyl-phenyl)-17 β -hydroxy-17 α -(3-hydroxy-1(2)-propenyl)-4,9-estradien-3-one
6	estrone sulfate	mifepristone
7	ethinyl estradiol	onapristone
8	estropipate	lilopristone
9	11-nitro estradiol	mifepristone

Various changes and modifications can be made in the present invention without departing from the spirit and scope thereof. The various embodiments which have been described and illustrated herein were intended to be representative and not limiting.

What is claimed is:

1. A method of hormone replacement therapy which comprises administering to a woman in need of such therapy, estrogen in an hormone replacement therapy effective amount and antiprogesterin in an amount which is effective both to inhibit estrogen-induced endometrial proliferation and to effect a state of substantial amenorrhea, in the absence of progestin administration.

2. The method of claim 1 in which the antiprogesterin is administered daily.

3. The method of claim 2 in which the administration is oral.

4. The method of claim 1 in which the estrogen and antiprogesterin are administered daily.

5. The administration of claim 1 in which the administration is oral.

6. The method of claim 1 in which each administration contains about 0.5 to 10 mg of the antiprogesterin daily.

7. The method of claim 6 in which the amount is about 1

to 5 mg.

8. The method of claim 1 in which the mode of administration is by depot.

9. The method of claim 1 in which the antiprogesterin is a progestin receptor antagonist.

10. The method of claim 9 in which the antiprogesterin is RU 486.

11. The method of claim 1 in which the administration extends over a minimum interval of 20 days.

12. In a method of hormone replacement therapy in which estrogen is administered in the absence of progestin administration to a woman in need of such therapy, the improvement which comprises the additional administration to said woman of antiprogesterin in an amount which both inhibits estrogen-induced endometrial proliferation and effects a state of substantial amenorrhea.

13. A kit containing at least 20 tablets, a portion of which contain a hormone replacement therapy effective amount of an estrogen and at least 20 of which contain an amount of an antiprogesterin which both inhibits estrogen-induced endometrial proliferation and effects a state of substantial amenorrhea.

14. The kit of claim 13 in which each tablet contains both the estrogen and antiprogesterin.

15. The kit of claim 14 in which the amount of antiprogesterin is about 0.5 to 10 mg.

16. The kit of claim 15 in which the amount of antiprogesterin is about 1 to 5 mg.

17. The kit of claim 16 in which the antiprogesterin is RU 486.

18. The kit of claim 13 in which the amount of antiprogesterin is about 0.5 to 10 mg.

19. The kit of claim 13 in which the amount of antiprogesterin is about 1 to 5 mg.

20. The kit of claim 13 in which the antiprogesterin is a progestin receptor antagonist.

* * * * *

United States Patent [19]**Hughes, Jr. et al.**[11] **Patent Number:** **5,770,226**[45] **Date of Patent:** **Jun. 23, 1998**[54] **COMBINED PHARMACEUTICAL
ESTROGEN-ANDROGEN-PROGESTIN ORAL
CONTRACEPTIVE**[75] Inventors: **Claude L. Hughes, Jr.**, Mebane;
Manuel J. Jayo, Winston-Salem, both
of N.C.[73] Assignee: **Wake Forest University**,
Winston-Salem, N.C.[21] Appl. No.: **679,764**[22] Filed: **Jul. 10, 1996**[51] Int. Cl.⁶ **A61K 9/20**[52] U.S. Cl. **424/464; 424/400; 424/465;**
514/841; 514/843[58] Field of Search **424/464, 465;**
514/841, 843[56] **References Cited****U.S. PATENT DOCUMENTS**

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[57]

ABSTRACT

Disclosed are methods and compositions for oral contraception. Certain compositions of the invention contain androgens, preferably methyltestosterone to be taken by younger users of the contraceptives to inhibit adverse effects of oral contraceptive use on bone mineral density.

22 Claims, No Drawings

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- What is claimed is:
1. A contraceptive preparation comprising a hormonal fraction consisting of an estrogen, a progestin and an andro-

gen in an amount effective to enhance bone accrual in a user of said contraceptive.

2. The preparation of claim 1, wherein said androgen is methyltestosterone.

3. The preparation of claim 2, further defined as comprising from about 0.2 mg to about 1.5 mg methyltestosterone per daily dose.

4. The preparation of claim 1, wherein said preparation is administered during about days 8-13 of a menstrual cycle.

5. The preparation of claim 1, wherein said progestin is about 0.050 mg levonorgestrel and said estrogen is about 0.030 mg ethinyl estradiol.

6. An oral contraceptive preparation comprising:

- (a) a composition comprising methyltestosterone, levonorgestrel and ethinyl estradiol to be administered daily from day 8 to about day 13 of a menstrual cycle;

- (b) a composition comprising levonorgestrel and ethinyl estradiol to be administered daily following day 13 of a menstrual cycle.

7. The preparation of claim 6, further comprising a placebo composition to be taken daily during days 1-7 of a menstrual cycle.

8. The preparation of claim 6, wherein the composition of (a) is further defined as comprising about 0.2 mg to about 1.5 mg methyltestosterone per daily dose.

9. The preparation of claim 8, wherein the composition of (a) is further defined as comprising about 0.050 mg levonorgestrel and about 0.030 mg ethinyl estradiol.

10. The preparation of claim 6, wherein the composition of (b) is further defined as:

- a first composition comprising about 0.075 mg levonorgestrel and about 0.040 mg ethinyl estradiol to be taken from day 14 to day 18 of a menstrual cycle; and

- a second composition comprising about 0.125 mg levonorgestrel and about 0.030 mg ethinyl estradiol to be taken from day 19 to day 28 of a menstrual cycle.

11. The preparation of claim 10, wherein the first composition, said second composition, or both are further defined as comprising about 0.25 mg to about 0.5 mg methyltestosterone per daily dose.

12. An oral contraceptive composition comprising from about 0.2 mg to about 1.5 mg methyltestosterone, about 0.050 mg levonorgestrel and about 0.030 mg ethinyl estradiol per daily dose.

13. An oral contraceptive composition formulated as 28 tablets as follows:

- a six tablets comprising about 0.2 mg to about 1.5 mg methyltestosterone, about 0.050 mg levonorgestrel and about 0.030 mg ethinyl estradiol;

- b) five tablets comprising about 0.075 mg levonorgestrel and about 0.040 mg ethinyl estradiol;

- c) ten tablets comprising about 0.125 mg levonorgestrel and about 0.030 mg ethinyl estradiol; and

- d) seven placebo tablets.

14. An oral contraceptive composition of claim 13 wherein composition (b), composition (c) or both further comprise 0.20 mg to 0.50 mg methyltestosterone per tablet.

15. The oral contraceptive composition of claim 13 wherein said tablets are contained in a dispenser comprising 28 compartments designed to hold one tablet each and wherein said dispenser provides a means to dispense said tablets in a defined order.

16. A method of enhancing bone accrual in a subject taking estrogen containing oral contraceptives wherein said subject has not attained peak bone mass, comprising administering an androgen to said subject in conjunction with said oral contraceptives.

United States Patent [19]
Koninckx[11] **Patent Number:** **5,827,843**
[45] **Date of Patent:** **Oct. 27, 1998**[54] **PREPARATION FOR SUBSTITUTION
THERAPY, CONTAINING AT LEAST ONE
PROGESTOGEN AND AT LEAST ONE
ESTROGEN**[75] **Inventor:** **Philippe Robert Marie Wilhelmus
Ghislain Koninckx, Bierbeek, Belgium**[73] **Assignee:** **Saturnus A.G., Luxembourg, Germany**[21] **Appl. No.:** **605,118**[22] **PCT Filed:** **Sep. 8, 1994**[86] **PCT No.:** **PCT/EP94/02997**§ 371 Date: **Jun. 4, 1996**§ 102(e) Date: **Jun. 4, 1996**[87] **PCT Pub. No.:** **WO95/07081****PCT Pub. Date: Mar. 16, 1995**[30] **Foreign Application Priority Data**

Sep. 9, 1993 [NL] Netherlands 9301562

[51] **Int. Cl.⁶** **A61K 31/56**[52] **U.S. Cl.** **514/170**[58] **Field of Search** 514/170[56] **References Cited****FOREIGN PATENT DOCUMENTS**

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Logsdon Orkin & Hanson, P.C.*[57] **ABSTRACT**

The invention relates to a preparation for substitution therapy and oral contraception comprising at least one progestogen and at least one estrogen in which the estrogen dose varies with a periodicity such that blood loss is substantially avoided, wherein the periodicity is preferably less than 10 days, more preferably less than 7 days, such as preparations containing the progestogen and/or estrogen in an oral, transdermal, parenteral and/or implantable application form.

9 Claims, No Drawings

PREPARATION FOR SUBSTITUTION THERAPY, CONTAINING AT LEAST ONE PROGESTOGEN AND AT LEAST ONE ESTROGEN

This application is a 371 of PCT/EP94/62997 filed Sep. 8, 1994.

The present invention relates to a preparation for substitution therapy and for oral contraception. More particularly the present invention on the one hand relates to relieving the effects which occur because the ovaries decrease or stop production of female hormones, for instance during the menopause. The substitution therapy is mainly intended to induce amenorrhoea with negligible blood loss.

During and after the menopause these effects comprise hot flushes and nocturnal sweating, atrophy of the vagina which can result in sexual difficulties, bone decalcification, increase in heart and blood vessel disorders and psychic symptoms with a causal connection that is usually difficult to demonstrate.

Up to the present different types of substitution therapy have been applied comprising a hormone treatment with one or more estrogens and one or more progestogens.

According to a first therapy, low doses of estrogens and progestogens are administered, but such a treatment is ineffective in respect of the decalcification and heart and blood vessel disorders.

In another therapy the natural cycle of estrogens and progestogens is followed as closely as possible. This treatment inevitably results in menstruation and has the advantage of a reduced risk of cancer of the uterus.

According to yet another therapy only estrogens are administered in a dose which lies below the threshold for menstrual bleeding. This treatment has the drawback however of an increased risk of cancer of the uterus.

According to a most recently known therapy estrogens and progestogens are administered continuous] such that the endometrium does not proliferate. This therapy has the drawback however of an unacceptably high incidence of slight, irregular blood loss.

The present invention has for its object to provide a substitution therapy wherein the above described drawbacks occur to a much lesser extent, with the objective of inducing amenorrhoea with negligible blood loss over a long period (many months to years).

On the other hand, the present invention relates to preparations designed for oral contraception with substantially continuous application.

In continuous application of oral contraceptive frequently intermediate bleedings occur. The preparations according to the present invention are designed to induce menstrual bleeding with a regular menstrual bleeding, with an extended cycle or eventually a constant amenorrhoea, but characterized by an optimal (cycle) control and/or by a substantially reduced occurrence of intermediate bleeding.

EP-A-559 240 discloses preparations for substitution therapy and oral contraception in which the estrogen dose is constant and the progestagen dose is periodically alternated.

However, the improvement in inhibiting endometrium bleeding is minor. Above that, since the use of higher progestogen doses provided better results than lower doses it appears illogical to use periodically varying estrogen doses.

The present invention is based on the finding that surprisingly when using periodically varying estrogen doses the occurrence of blood loss and intermediate bleeding is substantially avoided. The estrogen dose is herein oscillated

such that estrogen-dominant and progestogen-dominant periods occur alternatingly with a sufficiently short periodicity. This short periodicity in the estrogen dose is necessary to avoid blood loss.

Purely by administering a dose of progestogen or estrogen substantially constant in time and an estrogen or progestogen varying in time between at least two dose levels, it was possible to induce the desired amenorrhoea while no blood loss occurred over a longer period.

The invention therefore relates to a preparation for substitution therapy and for oral contraception comprising at least one progestogen and at least one estrogen in which the estrogen dose varies with a periodicity such that blood loss is substantially avoided.

It is noted that the preparation is formulated such that a substantially constant blood concentration is obtained for progestogen or estrogen, while the estrogen concentration in the blood varies between two blood concentrations. The periodicity must be sufficiently short and is generally less than 10 days. The periodicity is usually less than 7 days. The periodicity generally lies between 2-9 days, preferably between 2-6 days. It will however be apparent that the periodicity is dependent on the estrogens and progestogens used and the applied doses. Both the periodicity and concentrations of estrogen and progestogen are easy to determine by routine experimentation.

According to an embodiment of the invention the preparation contains a constant progestogen dose, while the estrogen dose oscillates between two levels. This preparation is recommended because there is a greater certainty of avoiding blood loss over a longer period.

According to another embodiment the preparation contains oscillating doses of progestogen and estrogen, in varying ratios however such that blood loss is avoided and amenorrhoea is induced.

Use can be made in general of all known progestogens, such as

progesterone	300-900 mg/day
norethisterone acetate	2-5 mg/day
medroxyprogesterone acetate	1-5 mg/day
d-norgestrel	30-150 µg/day
desogestrel	30-150 µg/day
norgestimate	30-150 µg/day
cyproterone acetate	0.2-2 mg/day
gestodene	10-150 µg/day
3-ketodesogestrel	10-150 µg/day
drospirenon	0.2-3.0 mg/day

or combinations thereof. It is noted that the preparation can contain one or more progestogens and estrogens.

It will be apparent that the quantity of progestogen and estrogen depends on the person (constitution and age), the progestogen(s) and estrogen(s), anti-progestogen and anti-estrogen for use and the form of administering same.

The progestogen and estrogen can each be present in an oral, transdermal, parenteral or implantable application form for substitution therapy. The preparation can for instance comprise an application form which contains the progestogen and estrogen, and a second like application form which contains the progestogen and an increased dose of estrogen. The progestogen and estrogen can of course be present in like but separate forms of application or in mutually differing forms of application. The progestogen can for instance be an implantable application form while the estrogens is administered orally, transdermally or parenterally in a dose which takes account of the required time period according to the invention.

The oral application form to be used comprises tablets, capsules, syrup, solutions. The transdermal forms of application comprise gels, plasters. Strips can for instance be used wherein tablets with progestogen and estrogens in the desired ratio and periodicity are arranged in time sequence. The parenteral application form comprises injection fluid and the like. The implantable application form comprises for example a known implantable sustained release preparation.

The preparations for oral contraceptive comprise estrogens and progestogens in common form.

Preparations according to the invention were administered over a period of 3–12 months to 40 women in the menopause. By making use of the combination preparations according to the invention a constant amenorrhoea could be obtained in the case of more than 90% of the women, wherein the clinical tolerance was perceived as optimal, wherein the woman did not discern any subjective difference between a fixed or changing estrogens dose with a periodicity of about one week.

Using the preparations according to the invention as oral contraceptive intermediate bleeding will be substantially reduced.

EXAMPLE 1

A preparation according to the invention comprised tablets of the type A which contained 10 gamma aethinyl-estradiol, 1 mg estradiol valerianate and 0.5 mg norethisterone, and tablets of the type B which contained 15 gamma instead of 10 gamma aethinyl-estradiol. By alternately administering the tablets A and B over a time period of 7 days an amenorrhoea could be induced without blood loss for a very long period of time.

EXAMPLE 2

A preparation according to the invention contained 1 mg norethisterone or 0.5 mg cyproterone acetate and 2 mg estradiol valerianate. The preparation moreover contained tablets of the type B having 3 mg instead of 2 mg estradiol valerianate. By using the preparation with alternate administering (4–5 days) of the tablets A and B or B and A an amenorrhoea could be induced without blood loss for a longer period of time.

EXAMPLE 3

A preparation according to the invention comprised tablets of the type A which contained 15 gamma aethinyl-estradiol and 1 mg estradiol valerianate and 1 mg norethisterone. The preparation moreover contained tablets of the type B having 1.5 mg instead of 1 mg norethisterone. By alternately administering the tablets A and B with a periodicity of 4–7 days an amenorrhoea could be induced without blood loss for a very long period of time.

EXAMPLE 4

A preparation according to the invention for oral contraceptive with optimal cycle control comprises tablets of type A comprising 20 μ g aethinyl-estradiol and 75 μ g gestoden. The preparation contained tablets of type B comprising 30 μ g instead of 20 μ g aethinyl-estradiol. Tablets A and B are used in four alternating periods of six days.

EXAMPLE 5

A preparation according to the invention for oral contraceptive with optimal cycle control comprises tablets of type A comprising 15 μ g aethinyl-estradiol and 75 μ g gestoden,

and tablets of type B comprising 25 μ g instead of 15 μ g aethinyl-estradiol. Tablets A and B are used in six alternating periods of four days.

In example 4 and 5 only aethinyl-estradiol is used in order to use a estrogen dose which is as low as possible. However, higher estrogen doses may be used. Instead of using a constant progestogen dose fluctuating doses may be used fluctuating simultaneously and/or progressively in view of the varying estrogen dose.

EXAMPLE 6

A preparation for oral contraceptive according to the invention comprises tablets of type A comprising 20 μ g aethinyl-estradiol and 75 μ g gestoden, and tablets of type B comprising 30 μ g aethinyl-estradiol and 75 μ g gestoden and 50 μ g onapristone. The tablets A and B are used in four alternating periods of each six days. After four periods the whole cycle is repeated without allowing a free period.

EXAMPLE 7

A preparation according to the invention for hormone substitution treatment comprises tablets of type A comprising 2 μ g estradiol valerianate and 50 μ g gestoden. The tablets of type B comprised 3 μ g estradiol valerianate and 25–100 μ g onapristone. By alternately administering the tablets A and B over a time period of seven days amenorrhoea could be induced without blood loss for a very long period of time.

It is obvious for a skilled person in the examples in association with intermittently given antiprogestogen or anti-estrogen can be alternated alone or simultaneous with estrogens and/or progestagens. For instance, the antiprogestagen is added in a constant dose to the actual and the above mentioned combinations of estrogens and progestagens in products for hormone replacement therapy and for contraception.

I claim:

1. Preparation for substitution therapy and for oral contraception comprising at least one progestogen and at least one estrogen having dosing means in association therewith wherein the progestogen dose is substantially constant and the estrogen dose varies to oscillate between an estrogen-dominant period and a progestogen-dominant period with a periodicity of less than 10 days such that blood loss is substantially avoided.

2. Preparation as claimed in claim 1, wherein said periodicity amounts to 2–9 days.

3. Preparation as claimed in claim 1, wherein the dose of progestogen is substantially constant and the dose of estrogen oscillates.

4. Preparation as claimed in claim 1, wherein the dose of progestogen and the dose of estrogen oscillate in such a dose ratio that blood loss is substantially avoided.

5. Preparation as claimed in claim 1, wherein the progestogen comprises

progesterone	300–900 mg/day
norethisterone acetate	0.2–5 mg/day
medroxyprogesterone acetate	1–5 mg/day
d-norgestrel	30–150 μ g/day
desogestrel	30–150 μ g/day
norgestimate	30–150 μ g/day
cyproterone acetate	0.2–2 mg/day,

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-continued

gestodene	10-150 μ g/day
3-ketodesogestrel	10-150 μ g/day
drospirenon	0.2-3.0 mg/day

or combinations thereof.

6. Preparation as claim 1, wherein the estrogens comprises

aethinylestradiol	5-15 gamma/day
oestradiol valerianate	1-4 mg/day
oestradiol	1-2 mg/day

6

-continued

conjugated oestrogen	0.3-1.25 mg/day
oestriol	1-4 mg/day,

or combinations thereof.

7. Preparation as claimed in claim 1, further comprising anti-progestogen.

8. Preparation as claimed in claim 1, further comprising anti-estrogen.

9. Preparation as claimed in claim 1, further containing the progestogen and/or estrogen in an oral, transdermal, parenteral and/or implantable application form.

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