

Industria y Comercio

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-022740- -00003-0000

Fecha: 2008-04-15 10:25:42 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYI Eve. 378 FASENACIONAL
Act. 400 OPOSIOBSERVTER Folios: 101

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A:

- | | |
|--|--|
| ☒ Patente de Invención. | ☐ Marca Colectiva. |
| ☐ Patente de Modelo de Utilidad. | ☐ Marca de Certificación. |
| ☐ Diseño Industrial. | ☐ Lema Comercial. |
| ☐ Esquema de Trazado para Circuitos Integrados. | |
| ☐ Marcas de Productos o Servicios. | |

②

Numero del expediente: 07-22740

Solicitante: LABORATORIOS LICONSA, S.A.

SOLICITUD
PUBLICADA

Apoderado: GERMAN CASTILLO GRAU

Título de la nueva creación o denominación del signo: "COMPOSICION
FARMACEUTICA QUE COMPRENDE DROSPIRENONA Y ETINILESTRAIDOL."

Gaceta: 587

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: <u>PROCAPS S.A</u>	IDENTIFICACIÓN C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual <u> </u> Numero <u>890.106.527-5</u>
	Dirección: <u>CALLE 80 No. 78B -201</u> Nacionalidad o Domicilio: <u>COLOMBIA</u> Lugar de Constitución: <u>BARRANQUILLA</u> Teléfono: <u>(571)3719900</u> Fax: <u>(571)3730818</u> E-mail: <u> </u>	
REPRESENTANTE O APODERADO	Nombre: <u>ELIANA ISAURA MORENO BOHORQUEZ</u> Dirección: <u>CARRERA 13 No. 119-95 OF 104</u> Teléfono: <u>(571)2131213</u> Fax: <u>(571)6121979</u> E-mail: <u>negocios@optimum-co.com</u>	IDENTIFICACIÓN C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual <u> </u> Numero <u>51.975.664</u> TP <u>83823</u>

④ FUNDAMENTOS DE LA OPOSICIÓN:

Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor:

Justificación:

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo reve-
lado, ya se encontraba en el estado de la técnica o es posible derivarlo de la misma tal y
como se demostrará en el capítulo "Fundamento de Hechos".

⑤ Comprobante de pago No. _____

Fecha _____

⑥ ANEXOS

- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuere el caso.
- ☒ Pruebas de los fundamentos de la oposición.
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso.
- ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: ELIANA ISAURA MORENO BOHORQUEZ

FIRMA: _____

C.C. 51.975.664

TP. 83823

70

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 07022740 ✓
Asunto : Oposición a la solicitud de patente de Invención
titulada "COMPOSICIÓN FARMACÉUTICA QUE
COMPRENDE DROSPIRENONA Y
ETINILESTRAIDOL"
Solicitante : LABORATORIOS LICONSA, S.A.
Opositora : PROCAPS S.A. ✓

Publicada en la Gaceta de la Propiedad Industrial

N° 587 del 18 de enero de 2008

Yo, *ELIANA ISAURA MORENO BOHORQUEZ*, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad *PROCAPS S.A.* conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley

71

y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "COMPOSICIÓN FARMACÉUTICA QUE COMPRENDE DROSPIRENONA Y ETINILESTRAIDOL", cuyo titular es LABORATORIOS LICONSA, S.A., y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos ~~productos~~ de mi representada, que contienen, en particular Drospirenona y/o Etinilestradiol. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

- 2.1. La solicitud objeto de la presente fue presentada el 7 de marzo de 2007, reivindicando prioridad bajo la solicitud EP20040103837 del 2004-08-09; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 587 del 18 de enero de 2008, cuya publicación internacional corresponde a la WO2006015956 del 2006-02-16.
- 2.2. La solicitud colombiana 07022740 objeto de la presente oposición, se refiere a una composición farmacéutica que comprende drospirenona y etinilestradiol en forma amorfa, adsorbidos sobre un soporte sólido terapéuticamente inerte, en combinación con excipientes farmacéuticamente aceptables, caracterizada porque la composición comprende cantidades mensurables del solvente volátil cloruro de metileno; caracterizada porque la composición comprende cantidades mensurables de ambos solventes volátiles: cloruro de metileno y metanol; en donde el soporte sólido inerte se selecciona de entre partículas del grupo compuesto por almidón de maíz, almidón pregelatinizado, lactosa, croscannelosa sódica, óxido de hierro amarillo y polivinilpirrolidona o de mezclas de uno o más de ellos, en combinación con excipientes farmacéuticamente aceptados; caracterizada porque por lo menos el 80% de la drospirenona y por lo menos el 80% del etinilestradiol se disuelven desde dicha composición dentro de los 20 minutos en un ensayo realizado en un aparato de

disolución de acuerdo con la Farmacopea de los Estados Unidos, Edición número 27, Aparato 2, en 900 ml de agua destilada a 37°C y agitados a 50 rpm. Adicionalmente, la solicitud se refiere a un método para preparar la composición farmacéutica de acuerdo con cualquiera de las reivindicaciones anteriores, que comprende las siguientes etapas: i) disolver drospirenona y etinilestradiol en un solvente volátil o mezcla de solventes volátiles, en donde por lo menos uno de los solventes volátiles es el cloruro de metileno, ii) opcionalmente agregar un poliniero soluble en agua, iii) mezclar hasta la disolución, iv) aplicar la solución resultante sobre un soporte de partículas sólidas terapéuticamente inertes y v) secar el adsorbato granulado obtenido; donde el solvente volátil es una mezcla de de cloruro de metileno y metanol; en donde la mezcla de cloruro de metileno y metanol es una mezcla de cloruro de metileno/metanol [9 a 4]:[3 a 0,5] y/y; en donde la mezcla de cloruro de metileno es una mezcla de cloruro de metileno/metanol 6:1 y/y.

- 2.3. En primera instancia, se debe advertir que las reivindicaciones 17 a 21 se refieren al uso y no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)”*, los usos no están contemplados como patentables; y, Artículo 20.- *“No serán patentables*

(...) 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". Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al uso no sería patentable.

2.4. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: "Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial". Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:

- D1: WO0115701 publicada el 8 de marzo de 2001.
- D2: WO0152857 publicada el 26 de julio de 2001.

2.5. Ahora bien, el documento D1 en la descripción revela una composición farmacéutica que comprende, como un primer agente activo de drospirenona en una cantidad correspondiente a una dosificación diaria, sobre la administración de la composición, de aproximadamente 2 mg a aproximadamente 4 mg, y, como un segundo agente activo, etinilestradiol en una cantidad correspondiente a una

dosificación diaria de aproximadamente 0.01 mg a aproximadamente 0.05 mg, juntos con uno o varios a portadores farmacéuticamente aceptables o excipientes. Particularmente en las página 4 línea 11 a 24 y ejemplo 2 así como reivindicaciones 1 y 2 y figura 1 revela una composición que contiene drospirenona y etinilestradiol, donde el compuesto es micronizado o esparcido en partículas de un vehículo inerte en el orden de acelerar la disolución. Por su parte el documento D2, revela en la descripción una composición farmacéutica que comprende como un primer agente activo, un estrógeno (o derivado natural o sintético del mismo) en cantidades suficientes para tratar enfermedades, desórdenes y síntomas asociados con niveles endógenos deficientes de estrógeno en mujeres, y como un segundo agente activo, 6 β , 7 β , 15 β , 16 β -dimetilen-3-oxo-17 α -preg-4-eno-20,17-carbolactona (drospirenona) en cantidades suficientes para proteger el endometrio de los efectos adversos del estrógeno, conjuntamente con un excipiente o portador farmacéuticamente aceptable. Según esta anterioridad D2, dicha composición farmacéutica comprende estradiol como un primer agente activo en cantidades que corresponden a una dosis diaria de 1 a 3 mg para tratar enfermedades, desórdenes y síntomas asociados con niveles endógenos deficientes de estrógeno en mujeres, y como un segundo drospirerona en cantidades suficientes que corresponden a una dosis diaria de 1 a 3,5 mg para proteger el endometrio de los efectos adversos del estrógeno, junto con un excipiente o portador

farmacéuticamente aceptable. Este documento D2 también advierte que es una preparación farmacéutica multi-fásica que consiste en un número de unidades de dosificación diarias separadamente envasadas e individualmente removibles dispuestas dentro de una unidad de envase destinadas a administración oral durante un periodo de al menos 21 días donde dichas unidades de dosificación diarias comprenden una combinación de estradiol en una cantidad en el rango de desde aproximadamente 0,1 a 5 mg y drospirenona en el rango de desde aproximadamente 0,25 a 6 mg. Por lo tanto además que la presente solicitud comprende un uso no patentable a luz de la norma colombiana, también revela una combinación que puede derivarse de manera evidente del arte anterior de manera evidente dado que estas anterioridades ya revelaban composiciones farmacéuticas que comprende drospirenona y etinilestradiol en combinación con excipientes farmacéuticamente aceptables y micronizado o esparcido en partículas de un vehículo inerte en el orden de acelerar la disolución, donde no puede ser un salto cualitativo el hecho de agregar cantidades mensurables de un solvente volátil de cloruro de metileno. Así las cosas, como lo evidencia dicho documento D1 en combinación con el documento D2, la presente invención no es patentable toda vez que la materia revelada no comprende altura o nivel inventivo, puesto que a partir de los documentos D1 y D2, es posible llegar a una composición que incluya los activos de drospirenona y etinilestradiol en

combinación con un solvente volátil de cloruro de metileno como lo define la presente solicitud objeto de oposición.

2.6. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 07022740 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

2.7. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.7.1. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *"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."* A la fecha de prioridad, 9 de agosto de 2004, a partir del documento D2 en combinación con D1, puede llegar de manera evidente a un compuesto farmacéutico que combine drospirenona y etinilestradiol en combinación con un solvente volátil de cloruro de metileno, sobre el cual busca protección en el capítulo reivindicatorio.

2.7.2. CARENCIA DE APLICACIÓN INDUSTRIAL La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean*

nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”.

La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman el método terapéutico y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos, no cumplen con el requisito de la aplicación industrial.

2.8. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“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.”.* La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

2.9. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **“COMPOSICIÓN FARMACÉUTICA QUE COMPRENDE DROSPIRENONA Y ETINILESTRAIDOL”**, cuyo titular es **LABORATORIOS LICONSA, S.A.**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 587 del 18 de enero de 2008.

42
79
1

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: WO0115701 publicada el 8 de marzo de 2001.
- D2: WO0152857 publicada el 26 de julio de 2001.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

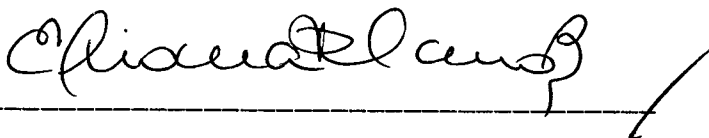
1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de **PROCAPS S.A.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:

- D1: WO0115701 publicada el 8 de marzo de 2001.
- D2: WO0152857 publicada el 26 de julio de 2001.

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,



ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.

82 15

03-13008342 024802 PROCAPS S.A.

Barranquilla, 08 de Abril de 2008

Hr:11:58:42

No. 12309293



***** Pag. 1
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
10*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

EN JUNIO DE ESTE AÑO SE ELEGIRÁ JUNTA DIRECTIVA DE LA CÁMARA DE COMERCIO. LAS INSCRIPCIONES DE CANDIDATOS DEBEN HACERSE EN LA PRIMERA QUINCENA DE MAYO. PARA INFORMACIÓN DETALLADA DIRIGIRSE A LA SEDE PRINCIPAL O COMUNICARSE AL SIGUIENTE TELEFONO: 3303911.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que por Escritura Pública No. 1,190 del 22 de Julio de 1976, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 28 de Julio de 1976 bajo el No. 6,070 del libro respectivo, fue constituida la sociedad----- limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA "PROCAPS LIMITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 1,307 del 28 de Junio de 1979, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Julio de 1979 bajo el No. 10,039 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.".-----

C E R T I F I C A

Que por Escritura Pública No. 3,810 del 31 de Dic/bre de 1980, otorgada en la Notaria Primera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 30 de Enero de 1981 bajo el No. 12,705 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad de responsabilidad limitada bajo al razon social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI - MITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 3,755 del 10 de Nov/bre de 1983, otorgada en la Notaria Unica de Soledad, inscrito(as) en esta Cámara de Comercio, el 22 de Nov/bre de 1983 bajo el No. 17,922 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.".-----

***** C O N T I N U A *****

CEPSA S.A. NIT 890 527 131-0

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

C E R T I F I C A

Que por Escritura Pública No. 3,615 del 06 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el No. 67,218 del libro respectivo, la sociedad antes mencionada----- cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A. -----

C E R T I F I C A

Que por Escritura Pública No. 3,775 del 18 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Enero de 1997 bajo el No. 67,704 del libro respectivo, la sociedad antes mencionada----- cambio de razon social, por la denominacion PROCAPS S.A. -----

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras y/o documentos privados:

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
39	1979/01/18	Notaria 3a. de Barranquilla.	9,452	1979/01/24
992	1981/04/30	Notaria 1a. de Barranquilla.	13,112	1981/05/06
1,464	1982/08/27	Notaria Unica de Soledad	15,533	1982/09/08
2,744	1983/08/18	Notaria Unica de Soledad	17,416	1983/08/26
3,826	1984/07/16	Notaria Unica de Soledad	19,554	1984/07/27
3,835	1985/08/26	Notaria Unica de Soledad	22,230	1985/09/04
2,260	1986/09/10	Notaria Unica de Soledad.	24,995	1986/09/15
1,849	1989/07/11	Notaria 2a. de Barranquilla.	33,909	1989/07/13
444	1990/02/21	Notaria 2a. de Barranquilla.	36,101	1990/03/16
3,090	1991/12/17	Notaria 2a. de Barranquilla	43,993	1992/01/28
269	1993/02/01	Notaria 2a. de Barranquilla	48,428	1993/02/16
2,342	1993/07/28	Notaria 2a. de Barranquilla	50,582	1993/08/10
3,652	1993/11/09	Notaria 2a. de Barranquilla	51,798	1993/11/22
3,615	1996/12/06	Notaria 2a. de Barranquilla	67,218	1996/12/20
89	1997/01/16	Notaria 2a. de Barranquilla	67,704	1997/01/23
2,070	1997/07/17	Notaria 2a. de Barranquilla	70,627	1997/07/31
2,281	1997/08/04	Notaria 2a. de Barranquilla	70,813	1997/08/14
765	1999/04/22	Notaria 3a. de Barranquilla	80,628	1999/04/23
459	2001/02/21	Notaria 2a. de Barranquilla	91,502	2001/02/23
2,608	2001/10/05	Notaria 2a. de Barranquilla	95,771	2001/11/08
1,730	2004/07/29	Notaria 2. de Barranquilla	112,999	2004/08/26
416	2005/03/03	Notaria 2. de Barranquilla	116,364	2005/03/10
1,613	2005/07/28	Notaria 2. de Barranquilla	119,322	2005/08/18

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad se rige por las siguientes disposiciones:

DENOMINACION O RAZON SOCIAL:

PROCAPS S.A.-----

SIGLA: PROCAPS.

***** C O N T I N U A *****



***** Pag. 2
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
10*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

DOMICILIO PRINCIPAL: Barranquilla.
NIT No: 890.106.527-5.
MATRICULA MERCANTIL: 24,802.

C E R T I F I C A

Direccion para notificaciones judiciales:
CL 80 No 78 B - 201.
De la ciudad de Barranquilla.

C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó hasta el 18 de Agosto de 2073.

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a)-La fabricacion de capsulas y otros productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas y cosmeticas, para uso y consumo humano y veterinario; b)-La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal; c)-La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, asi como la comercializacion interna y externa de los productos terminados, d) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos, quirurgicos, odontologicos, y hospitalarios para la salud humana y animal. e) La compra, venta, exportacion y distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. f) Actuar como representante o agente de personas naturales y juridicas, nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a), b), c). d) y e) antes descritos; g) Prestar los servicios de asesoria y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o in-

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCIÓN DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

dustrial; h)-Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto, comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables; comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles; designar representantes o apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o la de sus socios. La sociedad podra garantizar el cumplimiento de obligaciones adquiridas por terceros o por sus socios, para lo cual podra inclusive constituir gravámenes reales sobre sus bienes de cualquier naturaleza.-----

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acción
Autorizado		
\$*****2,000,000,000	*****2,000,000	*****1,000
Suscrito		
\$*****1,224,500,000	*****1,224,500	*****1,000
Pagado		
\$*****1,229,071,000	*****1,229,071	*****1,000

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad corresponde a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva. La sociedad tendra un Presidente, quien ejercera la representacion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. Ejercer la Representacion Legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir

***** C O N T I N U A *****



***** Pag. 3
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
10*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, disistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto. Las demas funciones que le correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendra las siguientes facultades entre otras. Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US\$150.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cuotas o partes de interes inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Vicepresidente tendra (1) suplente, designado por la Junta Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCIÓN DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

Directiva. El Suplente reemplazara al Gerente General, en sus faltas temporales, absolutas o meramente accidentales, quien junto con el gerente general, llevaran la representacion legal de la sociedad, con identicas facultades, pudiendolas ejercer conjunta o separadamente con el Presidente y Vicepresidente, con identicas facultades que el Gerente General y sin que sea necesario para ello acreditar la ausencia del titular. El Gerente General tendra las siguientes facultades entre otras: Ejercer la representacion legal de la sociedad, en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a Cincuenta Mil dolares de los Estados Unidos de America (US\$50.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente.

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.-----
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, y según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.-----
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE: JUNTA DIRECTIVA

Principales

1. Minski Gontovnik Ruben	CC.*****7,463,982
2. Minski Gontovnik Meyer	CC.*****7,461,324
3. Minski Gontovnik Jose	CC.*****8,671,834

Suplentes

1. Minski Zilberblum Elliot	CC.*****72,219,541
2. Minski Deitel Daniel	*****
3. Minski Sharon	PA.*990,212,082,805

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS

***** C O N T I N U A *****



***** Pag. 4
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
10*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Presidente.	
Minski Gontovnik Ruben	CC.*****7,463,982
Suplente del Presidente	
Minski Minski Abraham	CC.*****802,575
Vicepresidente	
Minski Gontovnik Meyer	CC.*****7,461,324
Suplente del vicepresidente	
Minski Gontovnik Jose	CC.*****8,671,834

C E R T I F I C A

Que según Acta No. 11 del 01 de Febrero de 2001 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 12 de Febrero de 2001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Gerente General.	
Uribe Ochoa Guillermo Luis	CC.*****70,073,754

C E R T I F I C A

Que según Acta No. 406 del 02 de Sep/bre de 2004 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 09 de Sep/bre de 2004 bajo el No. 113,263 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Gerente.	
Tanaka Tatekawa Walter	CC.*****16,251,923

C E R T I F I C A

Que según Acta No. 124 del 29 de Marzo de 1999 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 04 de Agosto de 1999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal Ppal.	
Vargas Pertuz Ana Isabel	CC.*****32,696,645

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCIÓN DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

C E R T I F I C A

Que según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Revisor Fiscal.	
Lozada Villareal Milena	CC.*****32,748,111

C E R T I F I C A

Que por Escritura Pública No. 2,784 del 07 de Dic/bre de 2007, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 20 de Dic/bre de 2007 bajo el No. 3,492 del libro respectivo,-----
y las inscripciones 3.492-1, 3.493, 3.494, 3.495, 3.496, 3.497, ----
3.498, 3.499, 3.500, 3.501, 3.502, 3.503, 3.504, 3.505, 3.506, ----
3.507, Consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, -----
obrando como Presidente y Representante Legal de la sociedad C.I. NATURMEGA S.A., que obrando en su condicion de Presidente y -----
Representante Legaql de la sociedad PROCAPS S.A., el presidente ----
debidamente facultado por los Estatutos Sociales y por el Maximo Organo Social, otorga los siguientes poderes: Otorgar poder -----
general, amplio y suficiente a los doctores JOSEFINA DEL CARMEN ----
MIELES BUELVAS CC.No.33.138.497; a MARCELA CARVAJALINO PAGANO -----
CC.No.22.579.748; CRISTINA VIOLI FRANCESCHINI CC.No.22.463.716, con
las facultades que se transcriben a continuacion: a.- Para que ----
representen a la sociedad PROCAPS S.A, ante todo tipo de -----
autoridades administrativas y jurisdiccionales, en asuntos de ----
naturaleza civil, laboral, comercial, penal, aduanera, cambiaria,
tributaria, policiva, administrativa y fiscal. b.- Contestar y ----
presentar demandas, requerimientos, recursos, pedir y aportar -----
pruebas, recibir, notificarse, ejercer la accion de tutela, -----
tramitar incidente de desacato, comparecer en los procesos que ----
cursen contra la sociedad, allanarse en nombre de la sociedad en
los asuntos que sean necesarios, transigir, desistir, sustituir,
renunciar y reasumir el poder. c.- La facultad expresa de -----
conciliar, por tanto pueden llegar a acuerdos conciliatorios, ----
transaccionales, judiciales o extrajudiciales o extrajudiciales,
cualquiera que sea su cuantia, para lo cual las apoderadas deben
aportar la autorizacion simple y escrita del Representante legal
de la sociedad. d.- Podran presentar solicitudes de devolucion y/o
compensacion de impuestos, ventas y rentas, recibir los pagos por
las devoluciones y adelantar todo tramite o proceso administrativo
ante la DIAN, de tal forma que en ningun momento quede sin -----
representacion legal de la sociedad. PODERES ESPECIALES: a.- Se ----
confiere poder especial amplio y suficiente a las personas que se
determinan seguidamente, que conforman el grupo A y B, para, para
que conjuntamente suscriban contratos de suministros de mercancías
y servicios con entidades oficiales, hasta la suma de OCHOCIENTOS

***** C O N T I N U A *****



***** Pag. 5
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
10*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA (US800.000.00), -----
liquidados a la tasa representativa del mercado vigente en el día
que se realice la respectiva transaccion. Grupo A. WALTER NANAKA
TATEKAWA CC.No.16.251.923, CLAUDIA TANGARIFE CASTILLO -----
CC.No.41.660.293, CARMEN ALICIA FLOREZ CC.No.22.434.044, IVAN -----
VILLAREAL CAMACHO CC.No.91.201.749, CARMEN ALICIA HERRERA -----
DIAZGRANADOS CC.No.22.377.540, DAVID ANTONIO CHARRIS GIRALDO -----
CC.No.19.341.274, RICARDO DORADO HURTADO CC.No.79.715.772, JAIME
FORERO LLINAS CC.No.19.300.593. b.- Se confiere poder especial -----
amplio y suficiente al señor WILLIAM ALBERTO BARROS CERRA -----
CC.No.8.715.941, y al señor ANTONIO VARELA DIAZ CC.No.72.004.699,
para que en nombre y representacion de PROCAPS S.A., suscriban -----
declaraciones cambiarias, aduaneras y tributarias a que este -----
obligada la sociedad, en el giro normal de sus negocios y -----
operaciones sociales, por tanto quedan facultados para firmarlas,
como tambien los demas documentos relacionados con ellas, -----
notificarse, aportar y solicitar las pruebas que sean necesarias.
c.-Otorgar poder especial amplio y suficiente al señor MARLON -----
TATIS PAREDES CC.No.72.176.874 y al señor WILLIAM ALBERTO BARROS
CERRA CC.No.8.715.941, para que en nombre y representacion de -----
PROCANPS S.A., suscriban las declaraciones, reportes y cualquier
documento relacionado con los tramites o registros de Comercio -----
Exterior y o cualquier entidad del Estado que haga sus veces: d)
Otorgar poder especial amplio y suficiente a la doctora CARMEN -----
ALICIA HERRERA DIAZGRANADOS, CC.No.22.377.540 y al doctor WALTER
TANAKA TATEKAWA, CC.No.16.251.923, para que en nombre y -----
representacion de PROCAPS S.A.; endosen los titulos valores de la
sociedad hasta por la suma de UN MIL MILLONES DE PESOS -----
(1.000.000.000.00) M.L. CUARTO: EI representante legal de la -----
sociedad PROCAPS S.A.; doctor RUBEN MINSKI GONTOVNIK, manifiesta
que la presente reforma fue aprobada por la Asamblea General -----
Extraordinaria de Accionista de PROCAPS S.A., con observancia de
las disposiciones legales y estatutarias.-----

C E R T I F I C A

Que en esta Cámara de Comercio no aparecen inscripciones posteriores
de documentos referentes a reforma, disolución, liquidación o
nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su última Renovación fue el: 19 de Marzo de 2008.

La información sobre embargos de establecimiento se suministra en

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCIÓN DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

Certificados de Matrícula, la de contratos sujetos a registro, en
Certificados Especiales.

m. l. g. a. s.

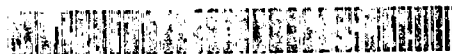
87

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800171099-2

RECIBO OFICIAL DE CAJA : 08 - 30,319
FECHA : ABRIL 15 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-022740- -00003-0000

Fe. rec: 2008-04-15 10:25:42 Dep. 2020 NULCREACIONE
Tra. 11 PATENTE E.Y. Eje 378 FASE NACIONAL I
Act. 400 OPOSICION OBSERVIER Folios: 101

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	NÚ. PAGO	FECHA PGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	4757293	09/04/2008	1.596.000.00

***** CONCEPTO *****

CANT. REENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04 PRESENTACION DE OBSERVACIONES	
	12 MARCAS Y LEMAS COMERCIALES	266.000.00
	TOTAL :	\$ 266.000.00

SON: DOSCIENTOS SESENTA Y SEIS MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.



PODER ESPECIAL

Yo, **WALTER TANAKA TATEKAWA**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. **07.022.740**, titulada "**COMPOSICION FARMACEUTICA QUE COMPRENDE DROSPIRENONA Y ETINILESTRAIDOL**", cuyo titular es **LABORATORIOS LICONSA, S.A.**, publicada en la gaceta No. 587 del 18 de Enero de 2008.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa y judicialmente todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Barranquilla (Colombia) a los 7 días del mes de Abril de 2008.

PROCAPS S.A.

C.C. N° 16'251.923

NIT: 890.106.527-5

Representante Legal

Acepto:

ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.

REPUBLICA DE COLOMBIA
NOTARIA SEGUNDA
2a.
MARTA L. ROJAS ZAMBRANO
Notaria Encargada
CIRCULO DE BARRANQUILLA

Alfred Russel

PRESENTACION PERSONAL
El anterior escrito fue presentado ante la
NOTARIA DIECIOCHO DEL CIRCULO DE BOGOTÁ, D.C.
personalmente por JUAN GARCIA
MORANO RODRIGUEZ
quien exhibió la c.c. 5975669 de 86
y Tarjeta Profesional No. 83823 C.S.A.
Fecha 14 ABR 2008


Gonzalo Espinel Quintana
NOTARIO (E)

X Edward Kins

ANEXO 1

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
8 March 2001 (08.03.2001)

PCT

(10) International Publication Number
WO 01/15701 A1

(51) International Patent Classification⁷: **A61K 31/565**,
31/585, A61P 15/00

(21) International Application Number: PCT/IB00/01213

(22) International Filing Date: 31 August 2000 (31.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
99202826.6 31 August 1999 (31.08.1999) EP
09/386,274 31 August 1999 (31.08.1999) US

(71) Applicant (for all designated States except US): **SCHERING AKTIENGESELLSCHAFT** [DE/DE]; D-13342 Berlin (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **HEIL, Wolfgang** [DE/DE]; Münchener Strasse 26/27, D-10825 Berlin (DE).
HILMAN, Jürgen [DE/DE]; Ugandastrasse 9, D-13351

Berlin (DE). **LIPP, Ralph** [DE/DE]; Holzungsweg 63, D-14169 Berlin (DE). **HEITHECKER, Renate** [DE/DE]; Wolzogenstrasse 15, D-14163 Berlin (DE).

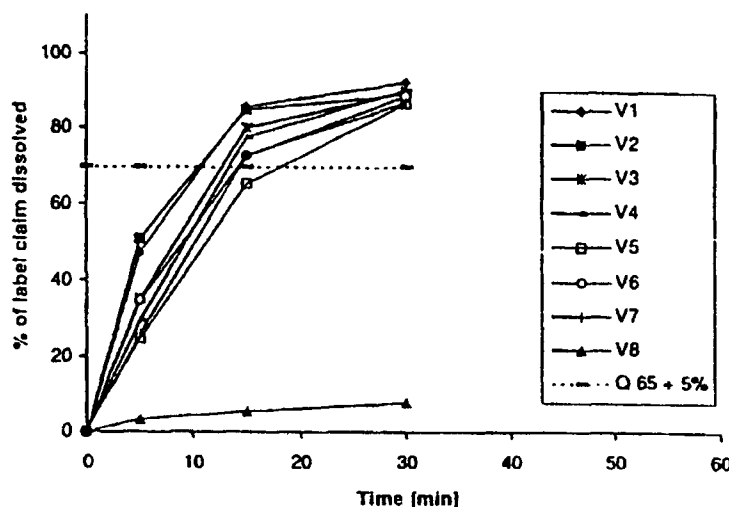
(74) Agent: **THORSEN, Jesper**; Plougmann, Vingtoft & Partners A/S, Sankt Annæ Plads 11, P.O. Box 3007, DK-1021 Copenhagen K (DK).

(81) Designated States (national): AE, AG, AL, AM, AT, AR (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KR (utility model), 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, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(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,

[Continued on next page]

(54) Title: PHARMACEUTICAL COMBINATION OF ETHINYLESTRADIOL AND DROSPIRENONE FOR USE AS A CONTRACEPTIVE



(57) Abstract: A pharmaceutical composition comprises, as a first active agent, 6 β , 7 β ; 15 β , 16 β -dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone (drospirenone) in an amount corresponding to a daily dosage, on administration of the composition, of from about 2 mg to about 4 mg, and, as a second active agent, 17 α -ethinylestradiol (ethinylestradiol) in an amount corresponding to a daily dosage of from about 0.01 mg to about 0.05 mg, together with one or more pharmaceutically acceptable carriers or excipients. In a specific embodiment, the composition consists of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 21 consecutive days, wherein said daily dosage units comprise the combination of drospirenone and ethinylestradiol. The composition may further comprise 7 or less daily dosage units containing no active agent or containing ethinylestradiol alone.

WO 01/15701 A1

25
91
WO 01/15701 A1



IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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

Published:

- With international search report.
- Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.

PHARMACEUTICAL COMBINATION OF ETHINYLESTRADIOL AND DROSPIRENONE FOR USE AS A CONTRACEPTIVE

FIELD OF THE INVENTION

- 5 The present invention relates to a pharmaceutical composition comprising drospirenone and ethinylestradiol, a method of providing dissolution of drospirenone, methods of inhibiting ovulation by administration of drospirenone and the use of drospirenone and ethinylestradiol for inhibiting ovulation.

10 BACKGROUND OF THE INVENTION

- Oral contraceptives containing a combination of a gestagen and an estrogen component have been used since the 1960's. The earliest contraceptive preparations consisted of 21 tablets containing the combination of active agents and 7 tablets containing no active agent, and the amount of each active agent was the same in each tablet (the so-called one-phase preparations). Subsequently, preparations were developed that consisted of tablets containing different amounts and ratios of the active agents over the cycle of administration (the so-called multiple-phase preparations).
- 15
- 20 Contraceptive reliability is mainly provided by the gestagen component. The daily dosage should be at least the minimum of what is needed for the gestagen in question to inhibit ovulation effectively. The estrogen component acts to increase the ovulation inhibitory effect of gestagen and to ensure cycle stability. Since the introduction of oral contraceptives, the daily dosage of gestagen has been reduced through the development of new and more efficient gestagens than were present in the earlier contraceptive preparations. It has also been possible to reduce the daily dosage of estrogen.
- 25

6 β ,7 β ;15 β ,16 β -dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone (drospirenone) is known from DE 26 52 761 in which its use as a diuretic compound is disclosed.

30

- In DE 30 22 337, the gestagen-like activity of the compound and its consequent utility as a contraceptive agent is described at dosage levels of 0.5-50 mg of drospirenone per day. It is also noted that the mechanism of action of the compound is very similar to that of the natural corpus luteum hormone progesterone, and that it does not give rise to increased blood pressure for which reason it may be administered to women who have or are at risk
- 35

of developing increased blood pressure. It is further described that drospirenone may be administered together with ethinylestradiol in an amount of 0.03-0.05 mg per day.

DE 30 51 166 discloses the use of the drospirenone for the treatment of gynaecological irregularities and for contraception at a dosage level of 0.5-50 mg per day.

EP 398 460 discloses the use of drospirenone for the treatment of androgen-induced disorders, aldosterone-induced disorders and hormonal irregularities as well as for contraception at dosage levels of 0.5-50 mg, preferably 1-10 mg per day. Ethinylestradiol may be co-administered at a level of 0.02-0.04 mg per day.

US 5,756,490 discloses pharmaceutical combination preparations comprising 23 or 24 dosage units containing a combination of a gestagen and an estrogen and 4-10 dosage units containing estrogen alone. Drospirenone is mentioned as a possible, but not preferred, gestagenic compound and ethinylestradiol is mentioned as a possible, but not preferred, estrogenic compound.

SUMMARY OF THE INVENTION

In the course of research leading to the present invention, it has surprisingly been found that a hitherto undisclosed minimum dosage level of drospirenone is required for reliable contraceptive activity. Similarly, a preferred maximum dosage has been identified at which unpleasant side effects, in particular excessive diuresis, may substantially be avoided.

Accordingly, in a first aspect, the present invention relates to a pharmaceutical composition comprising, as a first active agent, 6 β ,7 β ;15 β ,16 β -dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone (drospirenone) in an amount corresponding to a daily dosage, on administration of the composition, of from about 2 mg to about 4 mg, and, as a second active agent, 17 α -ethinylestradiol (ethinylestradiol) in an amount corresponding to a daily dosage of from about 0.01 mg to about 0.05 mg, together with one or more pharmaceutically acceptable carriers or excipients.

Apart from the active substances themselves, it is envisaged that an ester or prodrug of drospirenone may be employed in the present composition, e.g. an oxyiminopregnane

carbolactone as disclosed in WO 98/24801. Likewise, it is envisaged that esters or ethers of ethinylestradiol may be included in the composition.

- In a further aspect, the invention relates to a method of inhibiting ovulation in a mammal,
- 5 in particular a human, comprising administering, to said mammal, drospirenone in an amount in the range of from about 2 mg to about 4 mg of per day, together with ethinylestradiol in an amount of from about 0.01 mg to about 0.05 mg per day, said amounts being effective to inhibit ovulation in said mammal.
- 10 In a still further aspect, the invention relates to the use of drospirenone combined with ethinylestradiol for preparing a pharmaceutical preparation for the inhibition of ovulation in a mammal, in particular a human, the composition comprising an amount of drospirenone corresponding to a daily dosage, on administration of the composition, of from about 2 mg to about 4 mg, and comprising an amount of ethinylestradiol corresponding to a daily
- 15 dosage, on administration of the composition, of from about 0.01 to about 0.05 mg.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is further described with reference to the drawings in which

20

Fig. 1 is a graph showing the in vitro dissolution rate of drospirenone from tablet cores, V1-V7 being batches containing micronized drospirenone, and V8 being a batch containing macrocrystalline drospirenone;

- 25 Fig. 2 is a graph showing the in vitro dissolution rate of drospirenone from tablet cores, different lines representing different test batches;

Fig. 3 is a graph showing the in vitro dissolution rate of drospirenone from film-coated tablets, different lines representing different test batches;

30

Fig. 4 is a graph showing the in vitro dissolution rate of ethinylestradiol from tablet cores, different lines representing different test batches; and

- Fig. 5 is a graph showing the in vitro dissolution rate of ethinylestradiol from film-coated
- 35 tablets, different lines representing different test batches.

DETAILED DISCLOSURE OF THE INVENTION

27
95

Drospirenone, which may be prepared substantially as described in, e.g., US 4,129,564 or
5 WO 98/06738, is a sparingly soluble substance in water and aqueous buffers at various
pH values. Furthermore, drospirenone is rearranged to an inactive isomer under acid
conditions and hydrolysed under alkaline conditions. To ensure good bioavailability of the
compound, it is therefore advantageously provided in a form that promotes rapid
dissolution thereof.

10

It has surprisingly been found that when drospirenone is provided in micronized form (so
that particles of the active substance have a surface area of more than 10,000 cm²/g, and
the following particle size distribution as determined under the microscope: not more than
2 particles in a given batch with a diameter of more than 30 µm, and preferably ≤ 20
15 particles with a diameter of ≥ 10 µm and ≤ 30 µm) in a pharmaceutical composition, rapid
dissolution of the active compound from the composition occurs in vitro ("rapid
dissolution" is defined as the dissolution of at least 70% over about 30 minutes, in
particular at least 80% over about 20 minutes, of drospirenone from a tablet preparation
containing 3 mg of drospirenone in 900 ml of water at 37°C determined by the USP XXIII
20 Paddle Method using a USP dissolution test apparatus 2 at 50 rpm). Instead of providing
the drospirenone in micronized form, it is possible to dissolve it in a suitable solvent, e.g.
methanol or ethyl acetate, and spray it onto the surface of inert carrier particles followed
by incorporation of the particles containing drospirenone on their surface in the
composition.

25

Without wishing to be limited to any particular theory, it appears that the in vitro
dissolution rate of drospirenone is connected to the dissolution rate in vivo resulting in
rapid absorption of drospirenone in vivo on oral administration of the compound. This is
an advantage because isomerization of the compound in the gastric environment and/or
30 hydrolysis in the intestine is substantially reduced, leading to a high bioavailability of the
compound.

{ With respect to ethinylestradiol which is also a sparingly soluble substance, though less
sensitive to degradation than drospirenone under conditions prevailing in the
35 gastrointestinal tract, it is also an advantage to provide it in micronized form or sprayed

96 28
1 from a solution, e.g. in ethanol, onto the surface of inert carrier particles. This has the added advantage of facilitating a more homogenous distribution of the ethinylestradiol throughout the composition which might otherwise be difficult to obtain because ethinylestradiol is incorporated in extremely small amounts. When ethinylestradiol is
5 provided in micronized form, it preferably has the following particle size distribution as determined under the microscope: 100% of the particles have a diameter of $\leq 15.0 \mu\text{m}$, 99% of the particles have a diameter of $\leq 12.5 \mu\text{m}$, 95% of the particles have a diameter of $\leq 10.0 \mu\text{m}$, and 50% of the particles have a diameter of $\leq 3.0 \mu\text{m}$. Furthermore, no particle is larger than $20 \mu\text{m}$, and ≤ 10 particles have a diameter of $\geq 15 \mu\text{m}$ and $\leq 20 \mu\text{m}$.

10

To obtain a more rapid rate of dissolution, it is preferred to include carriers or excipients which act to promote dissolution of both active substances. Examples of such carriers and excipients include substances that are readily soluble in water such as cellulose derivatives, carboxymethylcellulose, hydroxypropyl cellulose, hydroxypropylmethyl
15 cellulose, gelled starch, gelatin or polyvinylpyrrolidone. In particular, it appears as though polyvinylpyrrolidone might be particularly helpful to promote dissolution.

The composition of the invention preferably comprises drospirenone in an amount corresponding to a daily dosage of from about 2.5 mg to about 3.5 mg, in particular about
20 3 mg. The amount of ethinylestradiol preferably corresponds to a daily dosage of from about 0.015 mg to about 0.04 mg, in particular from about 0.015 mg to about 0.03 mg. More particularly, the present composition comprises an amount of drospirenone corresponding to a daily dosage of from about 3.0 to about 3.5 mg and ethinylestradiol in an amount corresponding to from about 0.015 to about 0.03 mg.

25

Apart from its ability to inhibit ovulation, the composition of the invention has been found to possess pronounced anti-androgenic properties and may therefore be used in the prevention or treatment of androgen-induced disorders, in particular acne. Such use may be independent from or concomitant with the use as a contraceptive disclosed above.
30 Furthermore, since drospirenone is an aldosterone antagonist, it has diuretic properties and is therefore suitable for counteracting the water-retentive properties of ethinylestradiol.

In a particular embodiment, the invention relates to a pharmaceutical preparation
35 consisting of a number of separately packaged and individually removable daily dosage

units placed in a packaging unit and intended for oral administration for a period of at least 21 consecutive days, wherein each of said daily dosage units comprises a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg.

5

In one embodiment, the preparation further comprises 7 or less said daily dosage units containing no active agent. Alternatively, it is possible to include, in the dosage regimen, a period of 7 days or less during which no dosage units are ingested. For compliance reasons, however, it may be preferred to include an appropriate number of blanks in the
10 preparation, in which case the total number of daily dosage units in the preparation is at least 28. The inclusion of blanks, or the pill-free days, will then trigger withdrawal bleeding.

The preparation may be a one-phase composition, i.e. a preparation wherein the amounts
15 of either active agent remains constant for the entire at least 21-day period, or the amounts of either or both active agents may be varied over the at least 21-day period to generate a multiple-phase preparation, e.g. a two- or three-phase preparation, substantially as disclosed in, e.g., EP 148 724. In case of multiple-phase preparation, it may be possible to include a natural estrogen such as estradiol, e.g. in an amount of from
20 about 0.5 mg to about 4 mg per day, instead of ethinylestradiol.

In suitable embodiments of the present preparation, the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol may be 21, 22, 23 or 24, and the number of daily dosage units containing no active agent may then be 7, 6, 5 or 4,
25 as the case may be. In a further embodiment of the present preparation, the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol is 28, or a multiple of 28 such as 2-4, in particular 2 or 3, times 28.

In an alternative embodiment, the invention relates to a contraceptive preparation
30 consisting of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 28 consecutive days, wherein at least 21 of said daily dosage units comprises a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg, and wherein 7 or less of

said daily dosage units contain ethinylestradiol alone in an amount from about 0.01 to about 0.05 mg.

By including an appropriate number of dosage units comprising ethinylestradiol alone,
5 high contraceptive reliability, low follicular development and satisfactory cycle control with little or no intermenstrual bleeding may be obtained.

In this case, too, the preparation may be one in which the amounts of either active agent remains constant for the entire at least 21-day period (i.e. a two-phase preparation), or the
10 amounts of either or both active agents may be varied over the at least 21-day period to generate a multiple-phase preparation, e.g. a three- or four-phase preparation, substantially as disclosed in, e.g., EP 148 724. In case of multiple-phase preparation, it may be possible to include a natural estrogen such as estradiol, e.g. in an amount of from about 0.5 mg to about 4 mg per day, instead of ethinylestradiol.

15

In suitable embodiments of the present preparation, the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol may be 21, 22, 23 or 24, and the number of daily dosage units containing ethinylestradiol alone may then be 7, 6, 5 or 4, as the case may be.

20

In one embodiment of the present method of inhibiting ovulation, the method comprises administering, to said mammal, on each day of at least 21 consecutive days, a daily dosage unit comprising a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg, followed
25 by administering, on each day of 7 or less consecutive days, a daily dosage unit containing no active agent, or alternatively, administering no dosage units for 7 days or less.

In suitable embodiments of this method, the daily dosage units comprising the
30 combination of drospirenone and ethinylestradiol may be administered for 21, 22, 23 or 24 consecutive days, and the daily dosage units containing no active agent may then be administered for 7, 6, 5 or 4 consecutive days, as appropriate. Furthermore, the daily dosage units comprising the combination of drospirenone and ethinylestradiol may be administered for 28 consecutive days. In a variant of this embodiment, the daily dosage
35 units comprising the combination of drospirenone and ethinylestradiol are administered for

2-4, preferably 2 or 3, times 28 consecutive days, followed by administration of the daily dosage units comprising the combination of drospirenone and ethinylestradiol for 21, 22, 23 or 24 consecutive days and subsequently administration of the daily dosage units containing no active agent, or administration of no daily dosage units, for 7, 6, 5 or 4 consecutive days.

Alternatively, the present method comprises administering, on each day of at least 21 consecutive days, a daily dosage unit comprising a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg, followed by administering, on each day of 7 or less consecutive days, a daily dosage unit containing ethinylestradiol alone in an amount of from about 0.01 mg to about 0.05 mg.

In this alternative method, the daily dosage units comprising the combination of drospirenone and ethinylestradiol may suitably be administered for 21, 22, 23 or 24 consecutive days, and wherein the daily dosage units comprising ethinylestradiol alone may then be administered for 7, 6, 5 or 4 consecutive days, as appropriate. In a further embodiment of the method, the daily dosage units comprising the combination of drospirenone and ethinylestradiol are administered for 2-4, preferably 2 or 3, times 28 consecutive days, followed by administration of the daily dosage units comprising the combination of drospirenone and ethinylestradiol for 21 consecutive days and subsequently administration of the daily dosage units comprising ethinylestradiol alone for 7 consecutive days.

For use according to the invention, the pharmaceutical preparation may suitably be in the form of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 21 consecutive days, wherein each of said daily dosage units each comprises a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg.

As indicated above, the preparation may further comprise 7 or less daily dosage units containing no active agent (or may contain 7 or less empty "places", e.g. in the form of empty blisters in a blister pack, marking the days on which no daily dosage units are administered).

32
100

- Alternatively, the pharmaceutical preparation may be in the form of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 28 consecutive days, wherein at least 21 of said daily dosage units each comprises a combination of
- 5 drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount of from about 0.01 to about 0.05 mg, said packaging unit further comprising 7 or less daily dosage units comprising ethinylestradiol alone in an amount of from about 0.01 mg to about 0.05 mg.
- 10 The composition of the invention may be formulated in any manner known in the pharmaceutical art. In particular, as indicated above, the composition may be formulated by a method comprising providing drospirenone and, if desired, ethinylestradiol in micronized form in said unit dosage form, or sprayed from a solution onto particles of an inert carrier in admixture with one or more pharmaceutically acceptable excipients that
- 15 promote dissolution of the drospirenone and ethinylestradiol so as to promote rapid dissolution of drospirenone and preferably ethinylestradiol on oral administration. Examples of suitable excipients include fillers, e.g. sugars such as lactose, glucose or sucrose, sugar alcohols such as mannitol, sorbitol or xylitol, starch such as wheat, corn or potato starch, modified starch or sodium starch glycolate, lubricants such as talc,
- 20 magnesium stearate, calcium stearate, colloidal silica or stearic acid, and binders such as polyvinylpyrrolidone, cellulose derivatives, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose or gelatin, for making oral dosage forms such as tablets, pills or capsules.
- 25 Tablets may conveniently be coated with a suitable film-forming agent, e.g. hydroxypropylmethyl cellulose, hydroxypropyl cellulose or ethyl cellulose, to which a suitable excipient may optionally be added, e.g. a softener such as glycerol, propylene glycol, diethylphthalate or glycerol triacetate, filler such as sucrose, sorbitol, xylitol, glucose or lactose, a colorant such as titanium hydroxide, etc.
- 30 The present composition may also be formulated in liquid form, e.g. as a solution, suspension or emulsion, together with conventional diluents or excipients in a manner known per se in the pharmaceutical art.

5 A packaging unit comprising the daily dosage units described above may be prepared in a manner analogous to that of making other oral contraceptives. This may for instance be a conventional blister pack or any other form known for this purpose, for instance a pack comprising the appropriate number of dosage units (in this case at least 21, or for particular applications, 28 or a multiple of 28) in a sealed blister pack with a cardboard, paperboard, foil or plastic backing and enclosed in a suitable cover. Each blister container may conveniently be numbered or otherwise marked, e.g. starting with the first of the at least 21 dosage units that contain the combination of drospirenone and ethinylestradiol, optionally followed by 7 or less empty blisters or by the 7 or less dosage units that contain no active agent or that only contain ethinylestradiol (although the numbering may also start with the first of the 7 or less dosage units that only contain ethinylestradiol).

15 It is also envisaged that the present composition may be in the form of a parenteral formulation such as a subcutaneous implant or transdermal formulation. For making implants, the active agents may suitably be formulated together with one or more polymers that are gradually eroded or degraded when in use, e.g. silicone polymers, ethylene vinylacetate, polyethylene or polypropylene.

Where transdermal formulations are concerned, they may be prepared in the form of matrices or membranes or as fluid or viscous formulations in oil or hydrogels. For transdermal patches, an adhesive which is compatible with the skin should be included, such as polyacrylate, a silicone adhesive or polyisobutylene, as well as a foil made of, e.g. polyethylene, polypropylene, ethylene vinylacetate, polyvinylchloride, polyvinylidene chloride or polyester, and a removable protective foil made from, e.g., polyester or paper coated with silicone or a fluoropolymer. For the preparation of transdermal solutions or gels, water or organic solvents or mixtures thereof may be used. Transdermal gels may furthermore contain one or more suitable gelling agents or thickeners such as silicone, tragacanth, starch or starch derivatives, cellulose or cellulose derivatives or polyacrylic acids or derivatives thereof. Transdermal formulations may also suitably contain one or more substances that enhance absorption through the skin, such as bile salts or derivatives thereof and/or phospholipids. Suitable transdermal formulations may, for instance, be made in a manner analogous to that described in WO 94/04157 for 3-ketodesogestrel. Alternatively, transdermal formulations may be prepared according to a method disclosed in, e.g., BW Barry, "Dermatological Formulations, Percutaneous

Absorption", Marcel Dekker Inc., New York - Basel, 1983, or YW Chien, "Transdermal Controlled Systemic Medications", Marcel Dekker Inc., New York - Basel, 1987.

The present invention is further described in the following examples which are not in any way intended to limit the scope of the invention as claimed.

EXPERIMENTAL

Example 1

10

Preparation of tablets containing drospirenone and ethinylestradiol

Tablet cores of the following composition

15	micronized drospirenone	3.00 mg
	micronized ethinylestradiol	0.03 mg
	lactose monohydrate	48.17 mg
	corn starch	14.40 mg
	modified starch	9.60 mg
20	polyvinylpyrrolidone 25,000	4.00 mg
	magnesium stearate	0.80 mg

were prepared by charging a fluidized bed granulator with 31.68 kg corn starch, 21.12 kg modified starch, 6.60 micronized drospirenone, 0.066 kg micronized ethinylestradiol and 25 105.974 kg lactose monohydrate and activating the fluidized bed. An aqueous solution of 8.80 kg polyvinylpyrrolidone 25,000 in 46.20 kg purified water was sprayed continuously onto the fluidized bed while drying by heating the air stream of the fluidized bed. At the end of the process 1.76 kg magnesium stearate was sucked into the granulator and mixed with the granules by maintaining the fluidized bed. The resulting granulate was pressed 30 into tablet cores by compression using a rotary tablet press.

2.22464 kg of hydroxypropylmethylcellulose and 0.44528 macrogol 6000 were dissolved in 14.67 kg purified water. 0.44528 kg talc, 1.22430 kg titanium dioxide and 0.06050 kg ferric oxide pigment were suspended in 10.26 kg purified water with stirring and

homogenized. The solution and suspension were combined and used to coat the tablet cores by continuous application of the coating suspension in a coater.

Example 2

5

Dissolution of drospirenone from tablets

The rate of dissolution of drospirenone from the tablets prepared in Example 1 was determined by the USP XXIII Paddle Method using a USP Dissolution Test Apparatus 2 including 6 covered glass vessels and 6 paddles. Tablets were placed in 900 ml water at a temperature of 37°C ($\pm 0.5^\circ\text{C}$) and stirred at 50 rpm.

The results appear from Figs. 1, 2 and 4. From Fig. 1, it appears that the batch numbered V8 containing macrocrystalline drospirenone (but otherwise identical to the tablets prepared in Example 1) exhibited an extremely slow dissolution rate of drospirenone, whereas all batches containing micronized drospirenone exhibited a dissolution rate of more than 70% within 30 minutes.

Fig. 2 and Fig. 4 shows the results of dissolution of drospirenone from tablet cores and film-coated tablets, respectively. In both cases more than 70% of the active agent is dissolved within 30 minutes. Thus, the film coating did not significantly influence the rate of dissolution.

Example 3

Dissolution rate of ethinylestradiol from tablets in vitro

The rate of dissolution of ethinylestradiol from tablets prepared as described in Example 1 was determined according to the USP Paddle Method as described in Example 2 for drospirenone. The results appear from Figs. 3 and 5 showing the dissolution rates from tablet cores and film-coated tablets, respectively. In both cases, more than 70% of the active agent was dissolved within 30 minutes. Thus, the film coating did not significantly influence the rate of dissolution.

Example 4

Bioavailability of drospirenone and ethinylestradiol from tablets containing 3 mg of drospirenone and 0.03 mg ethinylestradiol

5

42 healthy women between 18 and 35 years of age were included in an open-label crossover study after their informed consent had been obtained. The aim of the study was to investigate the relative bioavailability of drospirenone and ethinylestradiol from a tablet formulation containing 3 mg drospirenone and 0.03 mg ethinylestradiol with reference to
10 an oral suspension containing 6 mg of drospirenone and 0.06 mg ethinylestradiol per vial.

The bioavailability was determined using serum concentrations of each active agent as parameters. Compared to the oral suspension, the relative bioavailability of drospirenone and ethinylestradiol from the tablets is 107% and 117%, respectively. It was therefore
15 concluded that both drospirenone and ethinylestradiol are completely released from the tablets in vivo.

The absolute bioavailability of drospirenone was determined in two studies to be 76%±13% after oral administration of 2 mg drospirenone to 8 young healthy women and
20 85%±24% after oral administration of a microcrystalline suspension containing 3.13 mg drospirenone to 6 postmenopausal women.

The oral bioavailability of ethinylestradiol was determined in several studies, and mean values of from 36% to 59% were reported in the literature, indicating a first-pass effect.
25

Example 5

Contraceptive efficacy of formulations containing drospirenone and ethinylestradiol

30 An open-label, randomized trial with 52 female volunteers aged 20-35 years whose informed consent had been obtained included 1 pre-treatment cycle, 3 treatment cycles with two different tablet containing 2 mg and 3 mg drospirenone, respectively, but otherwise corresponding to the tablets prepared in Example 1, and a follow-up phase. A wash-out phase of 1 month preceded the treatment.

35

At defined time points, selected central and peripheral parameters were investigated: LH, FSH, 17 β -estradiol, progesterone, cervical score, "spinnbarkeit", fern phenomenon. Ovarian function was checked by ultrasound. In addition, SHBG, CBG, prolactine, total testosterone, androstenedione, DHEA-S and selected metabolic parameters (serum
5 glucose, triglycerides, cholesterol, HDL, LDL) were examined. Blood pressure, heart rate, body weight and cycle control were documented.

The results of the study showed that both LH and FSH were clearly suppressed with both trial preparations. Accordingly, the secretion of estradiol and progesterone were greatly
10 reduced over all three treatment cycles with the exception of 3 volunteers receiving the 2 mg drospirenone preparation. This result was, in principle, confirmed by the accompanying ultrasound examinations. Follicular ripening occurred in several cases with both trial preparations. Although three ovulations were diagnosed with the preparation containing 2 mg drospirenone (one of which was described as "equivocal" and the other
15 as a "tablet-taking error"), no differences were demonstrable statistically ($p > 0.05$) between the two trial preparations as regards the hormones LH, FSH, estradiol and progesterone, and the parameter "ovulation during the treatment cycles". In keeping with the hormones, cervical function was greatly limited and the "spinnbarkeit" and crystallisability of the cervical mucus was greatly reduced with both trial preparations.
20 Prolactin increased minimally and SHBG and CBG distinctly with both preparations. Triglycerides and HDL levels increased with both trial preparations, while LDL levels decreased. Total cholesterol was largely unchanged in both treatment groups. Oral glucose tolerance remained virtually unchanged or was slightly decreased. Testosterone, androstenedione and DHEA-S decreased minimally.

25

The subjective and objective tolerance was good with both treatments. This was also the case for cycle control with the exception of the first cycle with 2 mg drospirenone. Blood pressure, heart rate and body weight remained constant in the majority of cases or showed a slight tendency to decrease.

30

After three months' treatment, it was concluded:

The two trial preparations were equally good as regards the subjective and objective tolerance.

~~58~~
106

No negative metabolic effects were observed with either preparation. HDL was influenced positively in the sense of an increase.

The results confirmed the results of earlier studies that the 2 mg drospirenone preparation was in the threshold region of ovulation inhibition, whereas the 3 mg drospirenone
5 preparation had a demonstrable ovulation-inhibiting effect in all cases examined.

CLAIMS

1. A pharmaceutical composition comprising, as a first active agent, 6 β ,7 β ;15 β ,16 β -dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone (drospirenone) in an amount
5 corresponding to a daily dosage, on administration of the composition, of from about 2 mg to about 4 mg, and, as a second active agent, 17 α -ethinylestradiol (ethinylestradiol) in an amount corresponding to a daily dosage of from about 0.01 mg to about 0.05 mg, together with one or more pharmaceutically acceptable carriers or excipients.
- 10 2. A composition according to claim 1 wherein the drospirenone is in micronized form or sprayed from a solution onto particles of an inert carrier.
3. A composition according to claim 1 or 2, comprising drospirenone in an amount corresponding to a daily dosage of from about 2.5 mg to about 3.5 mg, in particular about
15 3 mg.
4. A composition according to claim 1 wherein the ethinylestradiol is in micronized form or sprayed from a solution onto particles of an inert carrier.
- 20 5. A composition according to claim 1 or 4, comprising ethinylestradiol in an amount corresponding to a daily dosage of from about 0.015 mg to about 0.04 mg, in particular from about 0.02 mg to about 0.03 mg.
6. A composition according to any of the preceding claims, comprising an amount of
25 drospirenone corresponding to a daily dosage of from about 3.0 to about 3.5 mg and ethinylestradiol in an amount corresponding to from about 0.015 to about 0.03 mg, in particular comprising an amount of drospirenone corresponding to a daily dosage of about 3.0 mg and ethinylestradiol in an amount corresponding to a daily dosage of 0.03 mg.
- 30 7. A composition according to any of the preceding claims wherein the pharmaceutically acceptable carrier or excipient is selected so as to promote rapid dissolution of the first and second active agents.
8. A composition according to any of the preceding claims wherein at least 70% of the first
35 and second active substance are released within 30 minutes of administration thereof.

9. A composition according to claim 8, wherein at least 80% of the first and second active agents are released within 20 minutes of administration thereof.
- 5 10. A pharmaceutical preparation consisting of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 21 consecutive days, wherein said daily dosage units comprises a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg.
- 10 11. A preparation according to claim 10, which additionally comprises 7 or less daily dosage units containing no active agent intended for oral administration subsequent to the period of at least 21 consecutive days, the total number of daily dosage units being at least 28.
- 15 12. A preparation according to claim 10 or 11, wherein the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol is 21, 22, 23 or 24, and wherein the number of daily dosage units containing no active agent is 7, 6, 5 or 4.
- 20 13. A preparation according to claim 10, wherein the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol is 28, or a multiple of 28 such as 2-4, in particular 2 or 3, times 28.
14. A preparation according to claim 13, which additionally comprises a number of daily 25 dosage units comprising the combination of drospirenone and ethinylestradiol of 21, 22, 23 or 24, and a number of daily dosage units containing no active agent of 7, 6, 5 or 4.
15. A preparation according to any of claims 10-14, wherein the at least 21 daily dosage units comprise drospirenone and ethinylestradiol in micronized form or sprayed from a 30 solution onto particles of an inert carrier.
16. A preparation according to any of claims 10-15 wherein the at least 21 daily dosage units comprise drospirenone in an amount of from about 2.5 mg to about 3.5 mg, in particular about 3 mg, and ethinylestradiol in an amount of from about 0.015 mg to about 35 0.04 mg, in particular from about 0.015 mg to about 0.03 mg.

17. A preparation according to any of claims 10-16, wherein the at least 21 daily dosage units comprise drospirenone in an amount of from about 3.0 to about 3.5 mg and ethinylestradiol in an amount corresponding to from about 0.015 to about 0.03 mg.

5

18. A pharmaceutical preparation consisting of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 28 consecutive days, wherein at least 21 of said daily dosage units comprises a combination of drospirenone in an amount of from about 2
10 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg, and wherein 7 or less of said daily dosage units contain ethinylestradiol alone in an amount from about 0.01 to about 0.05 mg.

19. A preparation according to claim 18, wherein the number of daily dosage units
15 comprising the combination of drospirenone and ethinylestradiol is 21, 22, 23 or 24, and wherein the number of daily dosage units comprising ethinylestradiol alone is 7, 6, 5 or 4.

20. A preparation according to claim 18 or 19, wherein the at least 21 daily dosage units comprise drospirenone and ethinylestradiol in micronized form or sprayed from a solution
20 onto particles of an inert carrier.

21. A preparation according to any of claims 18-20, wherein the at least 21 daily dosage units comprise drospirenone in an amount of from about 2.5 mg to about 3.5 mg, in particular about 3 mg, and ethinylestradiol in an amount of from about 0.015 mg to about
25 0.04 mg, in particular from about 0.02 mg to about 0.03 mg.

22. A preparation according to any of claims 18-21, wherein the at least 21 daily dosage units comprise drospirenone in an amount of from about 3.0 to about 3.5 mg and ethinylestradiol in an amount corresponding to from about 0.015 to about 0.03 mg.

30

23. A method of inhibiting ovulation in a mammal, in particular a human, comprising administering, to said mammal, drospirenone in an amount in the range of from about 2 mg to about 4 mg of per day, together with ethinylestradiol in an amount of from about 0.01 mg to about 0.05 mg per day, said amounts being effective to inhibit ovulation in said
35 mammal.

24. A method according to claim 23, wherein the amount of drospirenone is in the range of from about 2.5 mg to about 3.5 mg, in particular about 3 mg of drospirenone per day.
- 5 25. A method according to claim 23, wherein the amount of ethinylestradiol is from about 0.015 mg to about 0.04 mg, in particular from about 0.015 to about 0.03 mg per day.
26. A method of preventing or treating androgen-induced disorders in a female mammal, in particular a female human, comprising administering, to said mammal, an amount of
- 10 drospirenone in the range of from about 2 mg to about 4 mg per day, together with an amount of ethinylestradiol of from about 0.01 mg to about 0.05 mg per day, said amounts being effective to prevent or treat androgen-induced disorders in said mammal.
27. A method according to claim 26, wherein the androgen-induced disorder is acne.
- 15 28. A method of inhibiting ovulation in a mammal, in particular a human, comprising administering, to said mammal, on each day of at least 21 consecutive days, a daily dosage unit comprising a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg, followed
- 20 by administering, on each day of 7 or less consecutive days, a daily dosage unit containing no active agent, or alternatively administering no daily dosage units for 7 or less consecutive days.
29. A method according to claim 28, wherein the daily dosage units comprising the
- 25 combination of drospirenone and ethinylestradiol are administered for 21, 22, 23 or 24 consecutive days, and wherein no daily dosage units or daily dosage units containing no active agent are administered for 7, 6, 5 or 4 consecutive days.
30. A method according to claim 28, wherein the daily dosage units comprising the
- 30 combination of drospirenone and ethinylestradiol are administered for 28 consecutive days.
31. A method according to claim 28, wherein the daily dosage units comprising the combination of drospirenone and ethinylestradiol are administered for 2-4, preferably 2 or
- 35 3, times 28 consecutive days, followed by administration of the daily dosage units

comprising the combination of drospirenone and ethinylestradiol for 21 consecutive days and subsequently administration of the daily dosage units containing no active agent, or alternatively no daily dosage units, for 7 consecutive days.

- 5 32. A method of inhibiting ovulation in a mammal, in particular a human, comprising administering, to said mammal, on each day of at least 21 consecutive days, a daily dosage unit comprising a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg, followed by administering, on each day of 7 or less consecutive days, a daily dosage unit
10 containing ethinylestradiol alone in an amount of from about 0.01 mg to about 0.05 mg.

33. A method according to claim 32, wherein the daily dosage units comprising the combination of drospirenone and ethinylestradiol are administered for 21, 22, 23 or 24 consecutive days, and wherein the daily dosage units comprising ethinylestradiol alone
15 are administered for 7, 6, 5 or 4 consecutive days.

34. A method according to claim 32, wherein the daily dosage units comprising the combination of drospirenone and ethinylestradiol are administered for 2-4, preferably 2 or 3, times 28 consecutive days, followed by administration of the daily dosage units
20 comprising the combination of drospirenone and ethinylestradiol for 21 consecutive days and subsequently administration of the daily dosage units comprising ethinylestradiol alone for 7 consecutive days.

35. A method of promoting rapid dissolution of drospirenone from a unit dosage form on
25 oral administration, the method comprising providing drospirenone in micronized form in said unit dosage form, or sprayed from a solution onto particles of an inert carrier in admixture with one or more pharmaceutically acceptable excipients that promote dissolution of the drospirenone.

- 30 36. Use of drospirenone combined with ethinylestradiol for preparing a pharmaceutical preparation for the inhibition of ovulation in a mammal, in particular a human, the composition comprising an amount of drospirenone corresponding to a daily dosage, on administration of the composition, of from about 2 mg to about 4 mg, and comprising an amount of ethinylestradiol corresponding to a daily dosage, on administration of the
35 composition, of from about 0.01 to about 0.05 mg.

37. Use according to claim 36, wherein the drospirenone is in micronized form, or sprayed from a solution onto particles of an inert carrier.
- 5 38. Use according to claim 36, wherein the amount of drospirenone corresponds to a daily dosage of from about 2.5 mg to about 3.5 mg, in particular about 3.0 mg.
39. Use according to claim 36, wherein the amount of ethinylestradiol corresponds to a daily dosage of from about 0.015 mg to about 0.04 mg, in particular from about 0.02 mg to
10 about 0.03 mg.
40. Use according to claim 36, wherein the ethinylestradiol is in micronized form, or sprayed from a solution onto particles of an inert carrier.
- 15 41. Use according to claim 36 for the prevention or treatment of androgen-induced disorders in a female mammal, in particular a female human.
42. Use according to claim 41, wherein the androgen-induced disorder is acne.
- 20 43. Use of a combination of drospirenone and ethinylestradiol for preparing a pharmaceutical preparation for the inhibition of ovulation in a mammal, in particular a human, the preparation being in the form of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 21 consecutive days, wherein said daily dosage
25 units each comprises a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg.
44. Use according to claim 43, wherein the preparation further comprises 7 or less daily dosage units containing no active agent, the total number of daily dosage units being at
30 least 28.
45. Use of a combination of drospirenone and ethinylestradiol for preparing a pharmaceutical preparation for the inhibition of ovulation in a mammal, in particular a human, the preparation being in the form of a number of separately packaged and
35 individually removable daily dosage units placed in a packaging unit and intended for oral

113

administration for a period of at least 28 consecutive days, wherein at least 21 of said daily dosage units each comprises a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount of from about 0.01 to about 0.05 mg, said packaging unit further comprising 7 or less daily dosage units comprising 5 ethinylestradiol alone in an amount of from about 0.01 mg to about 0.05 mg.

114

1/5

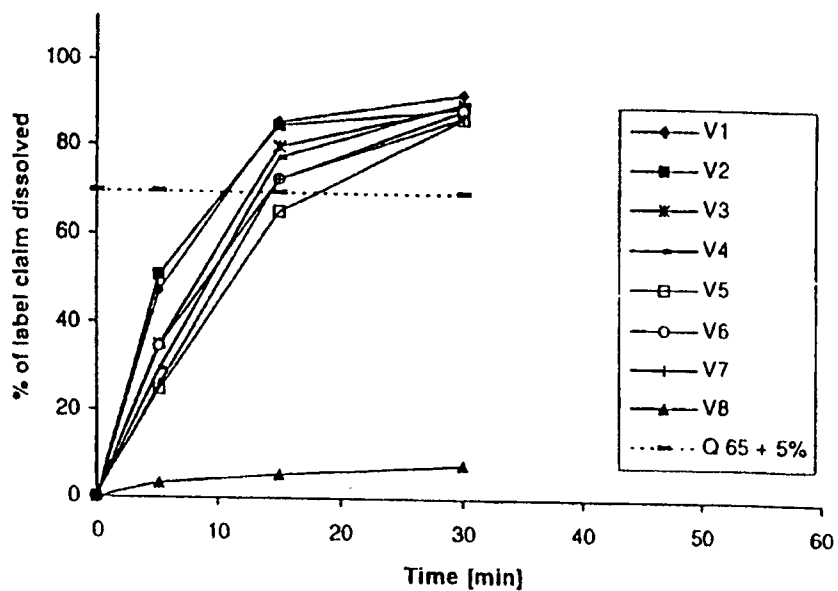


Fig. 1

115

2/5

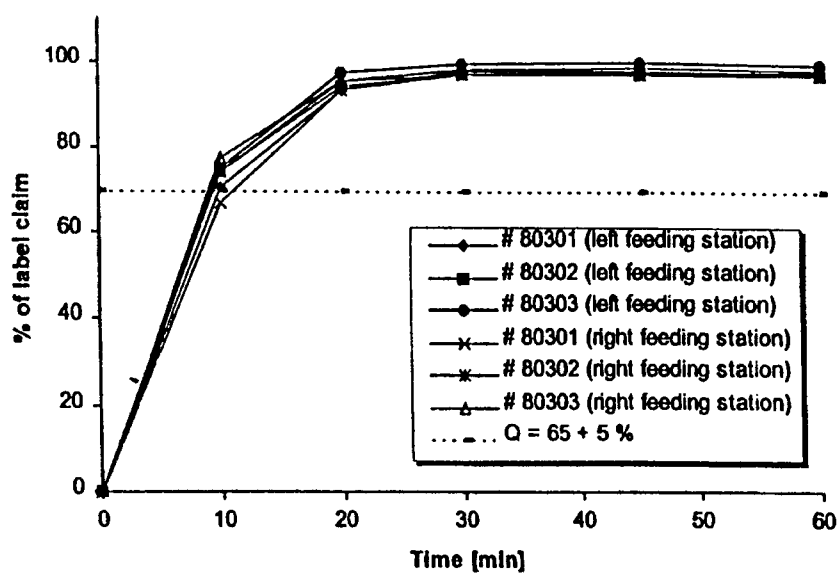


Fig. 2

52
116
1

3/5

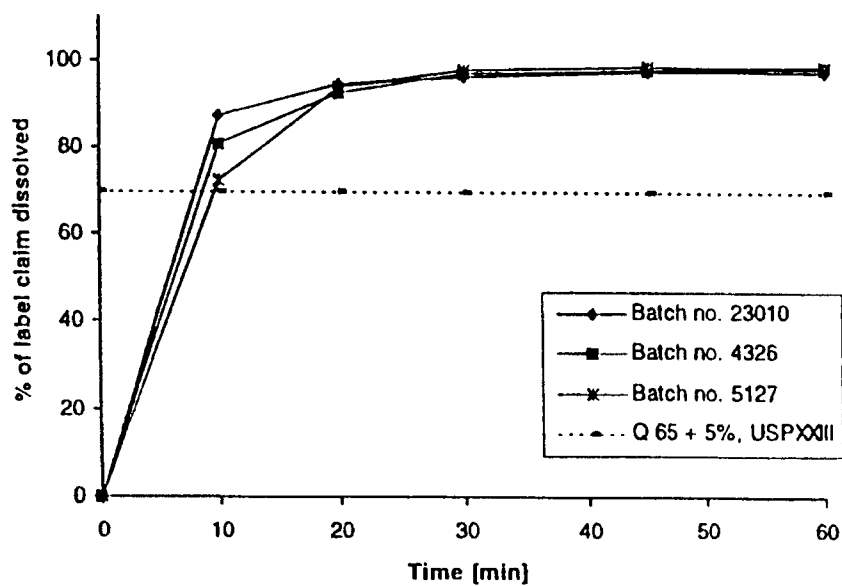


Fig. 3

4/5

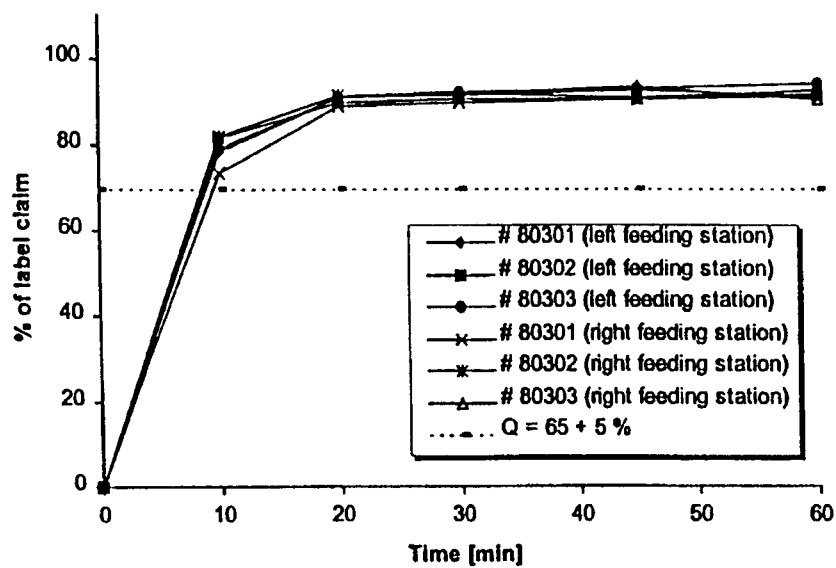


Fig. 4

5/5

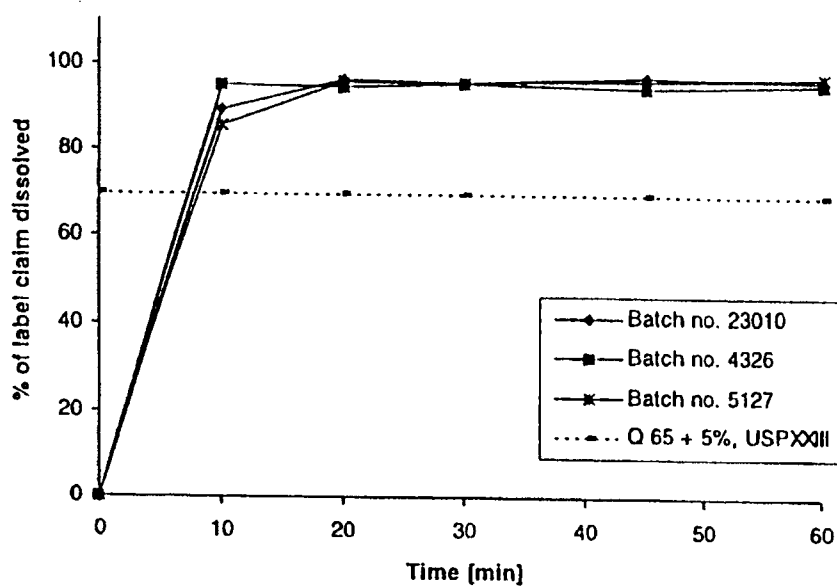


Fig. 5

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 00/01213

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/565 A61K31/585 A61P15/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 26730 A (SCHERING AG ;LACHNIT URSULA (DE); DUESTERBERG BERND (DE); SPONA JU) 12 October 1995 (1995-10-12) abstract; claims 1-4; example 1 ---	1,3,5,6, 10-14, 16-19, 21-26, 28-34, 36,38, 41,43-45
X	WO 98 04267 A (AMERICAN HOME PROD) 5 February 1998 (1998-02-05) abstract ----- -/--	1,3,5,6, 10-14, 16-19, 21-26, 28-34, 36,38, 41,43-45

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

16 January 2001

Date of mailing of the international search report

23/01/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Gonzalez Ramon, N

INTERNATIONAL SEARCH REPORT

58
120

International Application No

PCT/IB 00/01213

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 17194 A (SCHERING AG) 29 June 1995 (1995-06-29) abstract; claims 1,2,7,13 ---	1,3,5,6, 10-14, 16-19, 21-26, 28-34, 36,38, 41,43-45
X	WO 98 04269 A (AMERICAN HOME PROD) 5 February 1998 (1998-02-05) abstract page 9, line 20-25; claims 3,5,18-21,23,29 ---	1,3,5,6, 10-14, 16-19, 21-26, 28-34, 36,38, 41,43-45
X	WO 97 01342 A (SCHERING AG ;SCHMIDT GOLLWITZER KARIN (DE); KLEMMANN WALTER (DE)) 16 January 1997 (1997-01-16) abstract; claims 6-9,18,19,27-29,37-39; examples 1-3 ---	1,3,5,6, 10-14, 16-19, 21-26, 28-34, 36,38, 41,43-45
X	OELKERS W K H: "Effects of estrogens and progestogens on the renin-aldosterone system and blood pressure" STEROIDS: STRUCTURE, FUNCTION, AND REGULATION,US,ELSEVIER SCIENCE PUBLISHERS, NEW YORK, NY, vol. 61, no. 4, 1 April 1996 (1996-04-01), pages 166-171, XP004026568 ISSN: 0039-128X abstract; table 1 ---	1,3,5,6, 10-14, 16-19, 21-26, 28-34, 36,38, 41,43-45
X	OELKERS W ET AL: "EFFECTS OF A NEW ORAL CONTRACEPTIVE CONTAINING AN ANTIMINERALOCORTICOID PROGESTOGEN, DROSPIRENONE, ON THE RENIN-ALDOSTERONE SYSTEM, BODY WEIGHT, BLOOD PRESSURE, GLUCOSE TOLERANCE, AND LIPID METABOLISM" JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM,US,NEW YORK, NY, vol. 80, no. 6, 1 June 1995 (1995-06-01), pages 1816-1821, XP002046619 ISSN: 0021-972X see methods abstract ---	1,3,5,6, 10-14, 16-19, 21-26, 28-34, 36,38, 41,43-45

-/--

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 00/01213

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MUHN P ET AL.: "Drospirenone: a novel progestogen with antimineralocorticoid and antiandrogenic activity. Pharmacological characterization in animal models." CONTRACEPTION, (1995 FEB) 51 (2) 99-110., XP000908817	1,3,5,6, 10-14, 16-19, 21-26, 28-34, 36,38, 41,43-45
Y	abstract page 106	2,4,15, 20,35, 37,40
Y	----- NUERNBERG E.: "Manufacturing and properties of spray dried products!. HERSTELLUNG UND EIGENSCHAFTEN PHARMAZEUTISCHER SPRUHTROCKNUNGSPRODUKTE." ACTA PHARMACEUTICA HUNGARICA, (1978) 48/1 (19-35). CODEN: APHGAO, XP000908820 abstract page 33 -----	2,4,15, 20,35, 37,40

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 7-9

Present claims 7-9 relate to a carrier/excipient defined by reference to a desirable characteristic or property, namely "to promote rapid dissolution" without defining the chemical nature of said carrier/excipient. The claims cover all products/compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products/compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product/compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products/compounds specifically mentioned in the examples and the claims with due regard to the general idea underlying the present application

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

38
122

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 00/01213

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9526730 A	12-10-1995	DE 4411585 A	05-10-1995
		AU 722362 B	03-08-2000
		AU 1212799 A	25-03-1999
		AU 2073595 A	23-10-1995
		BG 100940 A	31-03-1998
		BR 9507251 A	02-09-1997
		CN 1159161 A	10-09-1997
		CZ 9602879 A	12-02-1997
		EP 0750501 A	02-01-1997
		FI 963831 A	29-11-1996
		HU 75521 A	28-05-1997
		JP 9511243 T	11-11-1997
		NO 964089 A	07-11-1996
		NZ 282824 A	28-07-1998
		PL 316569 A	20-01-1997
		SK 124396 A	07-05-1997
		US 5756490 A	26-05-1998
WO 9804267 A	05-02-1998	AU 3888697 A	20-02-1998
WO 9517194 A	29-06-1995	DE 4344462 A	29-06-1995
		CA 2179728 A	29-06-1995
		CN 1142185 A	05-02-1997
		CZ 9601861 A	11-12-1996
		EP 0735883 A	09-10-1996
		HU 74877 A	28-02-1997
		JP 9506888 T	08-07-1997
		NO 962676 A	22-08-1996
		NZ 278058 A	23-12-1998
		PL 315168 A	14-10-1996
		SK 83196 A	05-02-1997
		US 5583129 A	10-12-1996
		US 5824667 A	20-10-1998
WO 9804269 A	05-02-1998	AU 726091 B	02-11-2000
		AU 3888797 A	20-02-1998
		BR 9710566 A	17-08-1999
		CA 2261689 A	05-02-1998
		CN 1226168 A	18-08-1999
		EP 0956024 A	17-11-1999
		HU 9904344 A	28-05-2000
WO 9701342 A	16-01-1997	DE 19525017 A	02-01-1997
		AU 6352896 A	30-01-1997
		BR 9609317 A	06-07-1999
		CA 2225724 A	16-01-1997
		CZ 9704205 A	18-03-1998
		EP 0835114 A	15-04-1998
		HU 9900252 A	28-05-1999
		JP 11508538 T	27-07-1999
		NO 976067 A	27-02-1998
		NZ 312081 A	29-04-1999
		SK 178097 A	06-05-1998
		US 6027749 A	22-02-2000
		ZA 9605547 A	27-01-1997

ANEXO 2

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
26 July 2001 (26.07.2001)

PCT

(10) International Publication Number
WO 01/52857 A1

(51) International Patent Classification⁷: **A61K 31/585**,
A61P 5/30

(74) Agent: **THORSEN, Jesper**; Plougmann, Vingtoft & Partners A/S, Sankt Annæ Plads 11, P.O. Box 3007, DK-1021 Copenhagen K (DK).

(21) International Application Number: PCT/IB01/00041

(22) International Filing Date: 18 January 2001 (18.01.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
00200183.2 18 January 2000 (18.01.2000) EP
09/484,026 18 January 2000 (18.01.2000) US

(71) Applicant (for all designated States except US): **SCHERING AKTIENGESELLSCHAFT** [DE/DE]; Müllerstrasse 178, 13342 Berlin (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **HEIL, Wolfgang** [DE/DE]; Münchener Str. 26/27, 10825 Berlin (DE). **HILMANN, Jürgen** [DE/DE]; Ugandastr. 9, 13351 Berlin (DE). **LIPP, Ralph** [DE/DE]; Holzungsweg 63 D, 14169 Berlin (DE). **SCHÜRMANN, Rolf** [DE/DE]; Schottmüllerstr. 54. D, 14167 Berlin (DE).

(81) Designated States (national): AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), 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, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(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, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

with international search report

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



WO 01/52857 A1

(54) Title: **DROSPIRENONE FOR HORMONE REPLACEMENT THERAPY**

(57) Abstract: 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.

61
126**Drospirenone for Hormone Replacement Therapy**

FIELD OF INVENTION

- 5 The present invention relates to a pharmaceutical composition comprising drospirenone and estrogen, and to methods of hormone replacement therapy by administration of drospirenone and estrogen for estrogen-deficient women.

GENERAL BACKGROUND OF THE INVENTION

10

- The rise in life expectancy and consequent rise in the number of peri- and post-menopausal women has led to an increase in public and medical awareness of the climacteric period of transition in the reproduction phase of women. Menopause, the last menstruation, occurs between the ages of 45 and 55 in most women. Many factors, including race, genetics, nutrition, altitude, smoking, number of live births, the use of hormonal contraception, length of menstrual cycle and the age of onset of puberty have all been attributed, rightly or wrongly, to affect the age of the last menstrual period.

- During these phases of life, female endocrine activity undergoes a series of changes, with the result that the physical and psychological well being of many women is adversely affected. Hormone replacement therapy has aimed to improve the quality of life of women during this natural ageing process to alleviate symptoms associated with this time of transition and to reduce the likelihood or slow the progression of disorders and diseases associated with reduced hormonal activity.

25

Drospirenone is known from DE 26 52 761 in which its use as a diuretic is disclosed.

The gestagen-like activity of drospirenone and its consequent utility as a contraceptive agent at dosage levels of 0.5-50 mg is disclosed in DE 30 22 337.

30

The use and role of progestogens in opposed forms of hormone replacement therapy has been studied by the scientific community (Lobo R.A., 1992; Sobel N.B., 1994) as have been regimens comprising estrogens and progestogens (Corson S.L., 1993; Jones K.P., 1992).

35

62
127

The use of a preparation for substitution therapy and for oral contraception comprising at least one progestagen and at least one estrogen wherein the estrogen dose varies with a periodicity such that blood loss is substantially avoided is disclosed in PCT/EP94/02997.

5 SUMMARY OF THE INVENTION

The invention relates in a first aspect to 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
10 levels of estrogen in women, and as a second active agent, $6\beta,7\beta;15\beta;16\beta$ -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 pharmaceutically acceptable excipients or carriers.

15 In a second aspect, the invention relates to a pharmaceutical composition comprising as a first active agent estradiol in amounts corresponding to a daily dose of 1 to 3 mg to treat diseases, disorders and symptoms associated with deficient endogenous levels of estrogen in women, and as a second active agent $6\beta,7\beta;15\beta;16\beta$ -dimethylene-3-oxo- 17α -preg-4-ene-21,17-carbolactone (drospirenone) in amounts corresponding to a daily dose
20 of 1 to 3.5 mg to protect the endometrium from the adverse effects of estrogen, together with a pharmaceutically acceptable excipient or carrier.

Another aspect of the invention relates to the use of a combination of estrogen and drospirenone for the preparation of a medicament wherein the amount of estrogen is
25 sufficient to treat diseases, disorders and symptoms associated with deficient endogenous levels of estrogen in and the amount of drospirenone is sufficient to protect the endometrium from the adverse effects of estrogen.

In a further aspect, the invention relates to a method of treating diseases, disorders and
30 symptoms associated with deficient endogenous levels of estrogen in women comprising administering estrogen in sufficient amounts to alleviate said symptoms and drospirenone in sufficient amounts to protect the endometrium from adverse effects of estrogen.

Furthermore, the invention relates to a method of treating and preventing diseases,
35 disorders and symptoms associated with deficient endogenous levels of estrogen in

women comprising administering estradiol in amounts corresponding to daily doses of 1 to 3 mg, such as 1, 2 or 3 mg, and drospirenone in amounts corresponding to daily doses of 1 to 3.5 mg, such as 1, 1.5, 2, 2.5, 3, or 3.5 mg.

5 DETAILED DISCLOSURE OF THE INVENTION

In the present context, the term cycle itself or when associated with the term menstrual is intended to mean the number of days between menses in a woman. It can range from 21-31 days, typically 28 days.

10

In the present context, the term menopause is understood as the last natural (ovary - induced) menstruation. It is a single event and a result of an age-dependent dysfunction of the ovarian follicles. Menopause results from the ovaries decreasing their production of the sex hormones estrogen and progesterone. When the number of follicles falls below a

15 certain threshold (a bleeding threshold), the ovaries can no longer produce mature follicles and sex hormones. The ability to reproduce capability ends with menopause.

The peri-menopausal phase begins with the onset of climacteric symptoms when the cycle becomes irregular and ends one year after menopause. The end of peri-

20 menopausal phase can be identified after a protracted period of time without bleeding. Post-menopause is the phase that begins at menopause and continues until death.

One principal aim of hormone replacement therapy is to restore levels of the sex steroid hormones in naturally or prematurely pre-menopausal, menopausal and post-menopausal

25 women or to establish these levels in hypogonadal females.

Monotherapy, also referred to as unopposed therapy, is the treatment with estrogens alone. Exogenous estrogens stimulate the proliferation of the endometrium. In estrogen monotherapy, the opposing effect of progesterone, which terminates proliferation, is

30 absent. The desquamation phase, during which the top layers of the endometrium are shed, does not occur and proliferation of the endometrium occurs to a greater extent than in the phases up to and including the pre-menopausal phase. The result is hyperplasia, a risk factor for endometrial cancer.

Combination therapy, also referred to as opposed therapy, is a treatment where a progestagen is added to protect the endometrium from hyperplasia.

The use of natural progesterone in combination therapy is limited by the low bioavailability of natural progesterone, even in micronized form. Significantly, it has been found that combination therapy comprising the use of drospirenone as a progestagen, is remarkably effective. Drospirenone (DRSP), a 17- α -spiro lactone derivative, is a synthetic progestagen that has a surprisingly similar physiological profile to progesterone yet notably better bioavailability. It is the first synthetic progestagen to have a progesterone-like pharmacological profile in that it is antiestrogenic, antiandrogenic, and has antimineralcorticoid activity.

The invention embodies a pharmaceutical composition comprising 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, 6 β ,7 β ;15 β ;16 β -dimethylene-3-oxo-17 α -preg-4-ene-21,17-carbolactone (drospirenone) in sufficient amounts to protect the endometrium from the adverse effects of estrogen, together with pharmaceutically acceptable excipients or carriers.

Apart from the active substances themselves, it is envisaged that an ester or prodrug of drospirenone may be employed in the present composition, e.g. an oxyiminopregnane carbolactone as disclosed in WO 98/24801.

Deficient levels of estrogen can occur for a variety of reasons. The composition can be such that it is adequate for deficient levels of estrogen, regardless of the cause. Causes anticipated by the therapy are, but not limited to, natural menopause, peri-menopause, post-menopause, hypogonadism, castration or primary ovarian failure.

Low levels of estrogen, irrespective of the cause, lead to an overall decreased quality of life for women. Symptoms, diseases and disorders range from merely being inconvenient to life threatening. The composition of this therapy anticipates the effective alleviation of all physiological and psychological signs of estrogen deficiency.

Transient symptoms, such as vasomotor signs and psychological symptoms are certainly embodied with the realm of therapy. Vasomotor signs comprise but are not limited to hot flushes, sweating attacks such as night sweats, and palpitations. Psychological symptoms of estrogen deficiency comprise, but are not limited to, insomnia and other

5 sleep disorders, poor memory, loss of confidence, mood changes, anxiety, loss of libido, difficulties in concentration, difficulty in making decisions, diminished energy and drive, irritability, and crying spells.

The treatment of the aforementioned symptoms can be associated with the peri-

10 menopausal phase of a woman's life or after, sometimes long after menopause. It is anticipated that the invention is applicable to these and other transient symptoms during the peri-menopausal phase, menopause, or post-menopausal phase. Moreover, the aforementioned symptoms can be alleviated if the cause of the estrogen deficiency is hypogonadism, castration or primary ovarian failure.

15 In another embodiment of the invention, the therapy is used for the treatment of permanent effects of estrogen deficiency. Permanent effects comprise physical changes such as urogenital atrophy, atrophy of the breasts, cardiovascular disease, changes in hair distribution, thickness of hair, changes in skin condition and osteoporosis.

20 Urogenital atrophy, conditions associated with it such as vaginal dryness, increase in vaginal pH and subsequent changes in flora, or events which lead to such atrophy, such as decreases in vascularity, fragmentation of elastic fibres, fusion of collagen fibres, or decreases in cell volume are symptoms thought to be particularly relevant to this therapy.

25 Furthermore, the invention is thought to be relevant to other urogenital changes associated estrogen deficiency such as decreases in the length and/or diameter of the vagina, decreases mucus production, changes in cell population, decreases in glycogen production, decreases in growth of lactobacilli or increases in growth of streptococci, staphylococci, or coliform bacilli. Other associated changes that are thought to be

30 preventable by the invention are those that may render the vagina susceptible to injury or infection, such as exudative discharges, vaginitis, and dyspareunia. Furthermore, infections of the urinary tract and incontinence are other common symptoms associated with lowered estrogen levels.

Other embodiments of the invention include the prevention or alleviation of physical changes associated with estrogen deficiency, such as changes in the skin, changes in hair distribution, thickness of hair, atrophy of the breasts, or osteoporosis.

- 5 The prevention and management of osteoporosis, most notably post-menopausal osteoporosis, is a particularly interesting embodiment of the invention. Furthermore, bone demineralisation, reduction of bone mass and density, thinning and interruption of trabeculae, and/or consequent increase in bone fractures or bone deformations are thought to be particularly relevant. The prophylactic treatment of osteoporosis is an
10 interesting therapeutic application of the invention.

- A particularly interesting embodiment of the invention comprises the use of the composition for lessening the frequency, persistence, duration and/or severity of hot flushes, sweating attacks, palpitations, sleep disorders, mood changes, nervousness,
15 anxiety, poor memory, loss of confidence, loss of libido, poor concentration, diminished energy, diminished drive, irritability, urogenital atrophy, atrophy of the breasts, cardiovascular disease, changes in hair distribution, thickness of hair, changes in skin condition and osteoporosis, most notably hot flushes, sweating attacks, palpitations, sleep disorders, mood changes, nervousness, anxiety, urogenital atrophy, atrophy of the
20 breasts or for the prevention or management of osteoporosis.

- The pharmaceutical composition for HRT disclosed herein comprises estrogen. In preferred embodiments, the estrogen is selected from the group consisting of estradiol, estradiol sulfamates, estradiol valerate, estradiol benzoate, ethinyl estradiol, estrone,
25 estriol, estriol succinate and conjugated estrogens, including conjugated equine estrogens such as estrone sulfate, 17 β -estradiol sulfate, 17 α -estradiol sulfate, equilin sulfate, 17 β -dihydroequilin sulfate, 17 α -dihydroequilin sulfate, equilenin sulfate, 17 β -dihydroequilenin sulfate and 17 α -dihydroequilenin sulfate or mixtures thereof. Particularly interesting estrogens are selected from the group consisting of estradiol, estradiol sulfamates,
30 estradiol valerate, estradiol benzoate, estrone, and estrone sulfate or mixtures thereof, notably estradiol, estradiol valerate, estradiol benzoate and estradiol sulfamates. Most preferred are estradiol or estradiol sulfamates, particularly estradiol.

- Thought to be particularly relevant are micronized forms of estrogens, such as micronized
35 estradiol, micronized estradiol sulfamates, micronized estradiol valerate, micronized

estradiol benzoate, micronized estrone, or micronized estrone sulfate or mixtures thereof, notably micronized estradiol, micronized estradiol valerate, micronized estradiol benzoate or micronized estradiol sulfamates. Most preferred is micronized estradiol or micronized estradiol sulfamates, particularly micronized estradiol.

5

In certain embodiments of the invention, wherein the composition comprises more than one estrogen, one or more estrogen may be in micronized form, such as 2 or all of the estrogen.

- 10 Moreover, an interesting embodiment of the invention comprises a composition wherein the drospirenone (DRSP) is in micronized form, such that one or both estrogen and DRSP are in micronized form, preferably both estrogen and DRSP are in micronized form.

- Drospirenone, which may be prepared substantially as described in, e.g., US 4,129,564 or
15 WO 98/06738, is a sparingly soluble substance in water and aqueous buffers at various pH values. Furthermore, drospirenone is rearranged to an inactive isomer under acid conditions and hydrolysed under alkaline conditions. To ensure good bioavailability of the compound, it is therefore advantageously provided in a form that promotes rapid dissolution thereof.

20

- It has been found that when drospirenone is provided in micronized form in a pharmaceutical composition, rapid dissolution of the active compound from the composition occurs *in vitro*. A micronized substance is such that a test batch (ca. 200 mg) of the particles, herein drospirenone particles, has a surface area of more than 10,000
25 cm²/g, and has the following particle size distribution for drospirenone as determined under the microscope: not more than 2 particles in a given batch (ca. 200 mg) with a diameter of more than 30 µm, and preferably ≤ 20 particles with a diameter of ≥ 10 µm and ≤ 30 µm. The term "rapid dissolution" is defined as the dissolution of at least 70% over about 30 minutes, in particular at least 80% over about 20 minutes, of drospirenone
30 from a tablet preparation containing 3 mg of drospirenone in 900 ml of water at 37°C determined by the USP XXIII Paddle Method using a USP dissolution test apparatus 2 at 50 rpm.

- As an alternative to providing the drospirenone in micronized form, it is possible to
35 dissolve it in a suitable solvent, e.g. methanol or ethyl acetate, and spray it onto the

surface of inert carrier particles followed by incorporation of the particles containing drospirenone on their surface in the composition.

Without wishing to be limited to any particular theory, it appears that the *in vitro*

- 5 dissolution rate of drospirenone is connected to the dissolution rate *in vivo* resulting in rapid absorption of drospirenone *in vivo* on oral administration of the compound. This is an advantage because isomerization of the compound in the gastric environment and/or hydrolysis in the intestine is substantially reduced, leading to a high bioavailability of the compound.

10

- With respect to the estrogen which may also be a sparingly soluble substance, though usually less sensitive to degradation than drospirenone under conditions prevailing in the gastrointestinal tract, it is also an advantage to provide it in micronized form or sprayed from a solution, e.g. in ethanol, onto the surface of inert carrier particles. This has the
- 15 added advantage of facilitating a more homogenous distribution of the estrogen throughout the composition. When the estrogen is provided in micronized form, it preferably has the following particle size distribution as determined under the microscope: 100% of the particles have a diameter of $\leq 15.0 \mu\text{m}$, 99% of the particles have a diameter of $\leq 12.5 \mu\text{m}$, 95% of the particles have a diameter of $\leq 10.0 \mu\text{m}$, and 50% of the particles
- 20 have a diameter of $\leq 3.0 \mu\text{m}$. Furthermore, no particle is larger than $20 \mu\text{m}$, and ≤ 10 particles have a diameter of $\geq 15 \mu\text{m}$ and $\leq 20 \mu\text{m}$.

- The particle size distribution for estradiol or estradiol hemihydrate is preferably such that 100% of the particles in a given batch have a diameter less than $15.0 \mu\text{m}$, 99% have a
- 25 diameter less than $12.5 \mu\text{m}$, 95% have a diameter less than $10.0 \mu\text{m}$, 50% have a diameter less than $3.0 \mu\text{m}$, or 40% have a diameter less than $1.1 \mu\text{m}$.

- To obtain a more rapid rate of dissolution, it is preferred to include carriers or excipients, which act to promote dissolution of both active substances. Examples of such carriers and
- 30 excipients include substances that are readily soluble in water such as cellulose derivatives, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, gelled starch, gelatin or polyvinylpyrrolidone. In particular, it is anticipated that polyvinylpyrrolidone might be particularly helpful to promote dissolution.

69
134

The dose of the drospirenone in each composition is preferably such as to protect the endometrium from the adverse effects of estrogen. DRSP, in sufficient doses, may be used as an opponent to estrogen to protect the endometrium from hyperplasia or cancer.

- 5 In some cases, however, the dose of DRSP may be sufficient so as to stabilise the menstrual cycle and bleeding pattern. In such cases, doses of estrogen may be low or nil. Adipose tissue production of estrogen may be such that no or very low doses of estrogen are required to stabilise the menstrual cycle and bleeding pattern. Moreover, in certain embodiments, where the woman suffers from other disorders not compatible with the use
- 10 of an exogenous source of estrogen (such as for the absolute contraindications of severe liver diseases and pregnancy or for the relative contraindications endometrial carcinoma and endometriosis, mammary carcinoma, venous thromboembolism, hypertension, diabetes mellitus, otosclerosis and melanoma) no or very low amounts of estrogen may be in the composition. In such embodiments, the dose of DRSP may be such that the
- 15 disorder, disease, or symptom is alleviated.

- In preferred embodiments, the dose of DRSP corresponds to 15 to 70 mg per cycle, such as 20 to 60 mg per cycle, particularly 40 to 60 mg per cycle. The length of the cycle, as stated *supra* may vary from 21 to 31 days. Viewed otherwise, a composition may comprise
- 20 of an amount of DRSP corresponding to a daily dose ranging from 0.25 to 10, such as about 0.25 to 8, 0.25 to 6, 0.25 to 5, 0.5 to 4.5, 1 to 4, and 1.5 to 3.5 mg.

- The dose of estrogen may vary from woman to woman, depending on the phase of her life (peri-menopausal or post-menopausal), endogenous levels of estrogen, the severity of the
- 25 symptom(s), disorder or disease, the disorder, disease or symptom targeted, the use by the woman of other medicaments for other purposes, and other pharmacokinetic variables.

- In other embodiments, the dose of estrogen and/or DRSP is sufficient to treat hot flushes,
- 30 sweating attacks, palpitations, sleep disorders, mood changes, nervousness, anxiety, poor memory, loss of confidence, loss of libido, poor concentration, diminished energy, diminished drive, irritability, urogenital atrophy, atrophy of the breasts, cardiovascular disease, changes in hair distribution, thickness of hair, changes in skin condition or for the prevention or management of osteoporosis.

20 The dose of estrogen and/or DRSP may depend on the treatment, be it for endometrial protection such as bleeding pattern, for osteoporosis prevention or management, for the treatment of menopausal symptoms, such as the for the reduction in the number, frequency, and severity of hot flushes, night sweats, mood swings palpitations, insomnia
5 and other sleep disorders, mood changes, nervousness, anxiety, poor memory, loss of confidence, loss of libido, poor concentration, diminished energy, diminished drive and irritability.

In embodiments wherein the estrogen is estradiol, the amount of estradiol corresponds to
10 a daily dose ranging from 0.1 to 5 mg, such as about 0.2 to 4.5, 0.5 to 4, 1 to 3, in particular 1, 2, or 3 mg.

With regards to the doses of estradiol derivatives with greater potency, e.g. estradiol valerate, the comparable dosage may be calculated by adjusting the above-mentioned
15 dosages in accordance to the relative potency.

In embodiments where the woman is peri-menopausal the dose of estrogen and/or DRSP may depend on the day of the cycle, that is, whether she is in the preovulatory or postovulatory phase of the cycle, and how advanced within each phase. In embodiments
20 where the woman is post-menopausal or even pre-menopausal, the dose of estrogen and/or DRSP may depend on the time since the last menstruation.

In certain embodiments of the invention, the medicament is administered in the form a of a number of separately packaged and individually removable dosage units placed in a
25 packaging unit and intended for oral administration for a period of at least 21, such as at least 28 days, such as at least 30 or 31 days. In such embodiments, the dose of DRSP and/or estrogen may be the same within each dosage unit or may vary. In embodiments where the amount of DRSP and/or estrogen in the dosage unit varies according to the phase or day within the period of at least 21 days, such as at least 28 days that said
30 dosage unit is to be administered, such compositions, methods of treatments and preparations are termed multi-phased.

The dose proportionality may vary according to its use. In preferred embodiments the dose proportionality of estrogen and drospirenone for the preparation of a medicament is
35 such that estrogen doses are to treat diseases, disorders and symptoms associated with

deficient endogenous levels of estrogen and the amount of drospirenone is sufficient to protect the endometrium from the adverse effects of estrogen.

In preferred embodiments, the dose proportionality is sufficient to treat hot flushes, sweating attacks, palpitations, sleep disorders, mood changes, nervousness, anxiety, poor memory, loss of confidence, loss of libido, poor concentration, diminished energy, diminished drive, irritability, urogenital atrophy, atrophy of the breasts, cardiovascular disease, changes in hair distribution, thickness of hair, changes in skin condition or for the prevention or management of osteoporosis.

10

The invention relates to a method of treating diseases, disorders and symptoms associated with deficient endogenous levels of estrogen in women comprising administering estrogen in sufficient amounts to alleviate said symptoms and drospirenone in sufficient amounts to protect the endometrium from adverse effects of estrogen.

15 Preferably, the deficient levels of estrogen to which the method applies are caused by natural menopause, peri-menopause, post-menopause, hypogonadism, castration or primary ovarian failure.

The diseases, disorders and symptoms to which the method applies comprise hot flushes, sweating attacks, palpitations, sleep disorders, mood changes, nervousness, anxiety, poor memory, loss of confidence, loss of libido, poor concentration, diminished energy, diminished drive, irritability, urogenital atrophy, atrophy of the breasts, cardiovascular disease, changes in hair distribution, thickness of hair, changes in skin condition or for the prevention or management of osteoporosis. Specifically, the method is anticipated to apply to hot flushes, sweating attacks, palpitations, sleep disorders, mood changes, nervousness, anxiety, urogenital atrophy, atrophy of the breasts or for the prevention or management of osteoporosis.

The method applies to the administration of an estrogen, preferably estradiol, estradiol sulfamates, estradiol valerate, estradiol benzoate, ethinyl estradiol, estrone, estriol, estriol succinate and conjugated estrogens, including conjugated equine estrogens such as estrone sulfate, 17 β -estradiol sulfate, 17 α -estradiol sulfate, equilin sulfate, 17 β -dihydroequilin sulfate, 17 α -dihydroequilin sulfate, equilenin sulfate, 17 β -dihydroequilenin sulfate and 17 α -dihydroequilenin sulfate or mixtures thereof, most estradiol, estradiol

32
137

sulfamates, estradiol valerate, estradiol benzoate, estrone, and estrone sulfate or mixtures thereof, particularly estradiol.

A particularly attractive embodiment of the invention comprises the administration of
5 drospirenone (DRSP) and/or the estrogen in micronized form. Furthermore, of particular interest is where the estrogen is estradiol in micronized form. In such embodiments, one or both active ingredients are administered in micronized form.

In certain embodiments, the method comprises the administration of a dose of DRSP
10 corresponding to 15 to 70 mg per cycle, such as 20 to 60 mg per cycle, particularly 40 to 60 mg per cycle. The method preferably comprises the administration a dose of DRSP the amount of DRSP corresponding to a daily dose ranging from 0.25 to 10 mg, such as about 0.25 to 8, 0.25 to 6, 0.25 to 5, 0.5 to 4.5, 1 to 4, or 1.5 to 3.5 mg.

15 The amount of estradiol administered may correspond to a daily dose ranging from 0.1 to 5 mg, such as about 0.2 to 4.5, 0.5 to 4, 1 to 3, in particular 1, 2 or 3 mg.

A particularly pertinent embodiment relates to a pharmaceutical composition comprising, as a first active agent, estradiol in amounts corresponding to a daily dose of 1 to 3 mg to
20 treat diseases, disorders and symptoms associated with deficient endogenous levels of estrogen in women and as a second active agent $6\beta,7\beta;15\beta;16\beta$ -dimethylene-3-oxo-17 α -preg-4-ene-21,17-carbolactone (drospirenone) in amounts corresponding to a daily dose of 1 to 3.5 mg sufficient amounts to protect the endometrium from the adverse effects of estrogen together with a pharmaceutically acceptable excipient or carrier.

25

Certain preferred combinations with regards to the active ingredients in the composition, wherein the estrogen is estradiol comprise 1 mg of estradiol with 0.5 mg of DRSP, 1 mg of estradiol with 1 mg of DRSP, 1 mg of estradiol with 1.5 mg of DRSP, 1 mg of estradiol with 2 mg of DRSP, 1 mg of estradiol with 2.5 mg of DRSP, 1 mg of estradiol with 3 mg of
30 DRSP, 2 mg of estradiol with 1 mg of DRSP and 2 mg of estradiol with 4 mg of DRSP.

In a preferred embodiment, a preferred embodiment of the invention relates to a pharmaceutical composition comprising as a first active agent estradiol in amounts corresponding to a daily dose of 1 to 3 mg, such as 1, 1.5, 2, 2.5, or 3 mg of estradiol, and
35 as a second active agent $6\beta,7\beta;15\beta;16\beta$ -dimethylene-3-oxo-17 α -preg-4-ene-21,17-

carbolactone (drospirenone) in amounts corresponding to a daily dose of 1 to 3.5 mg, such as 1, 1.5, 2, 2.5, 3, or 3.5 mg of DRSP, together with a pharmaceutically acceptable excipient or carrier.

- 5 Accordingly, a preferred embodiment of the invention relates to a method of treating and preventing diseases, disorders and symptoms associated with deficient endogenous levels of estrogen in women comprising administering estradiol in amounts corresponding to daily doses of 1 to 3 mg, such as 1, 2 or 3 mg, and drospirenone in amounts corresponding to daily doses of 1 to 3.5 mg, such as 1, 1.5, 2, 2.5, 3, or 3.5 mg.
- 10 Given that deficient endogenous levels of estrogens may be associated with, amongst other conditions, natural menopause, peri-menopause, post-menopause, hypogonadism, castration or primary ovarian failure, the method of treating and preventing associated diseases, disorders and symptoms may persist until the death of the individual. That is to
- 15 say that the composition may be administered from the diagnosis of the disease, disorder or symptoms for the entirety of the individual's life. In certain embodiments, the method and the composition may be based on rhythm of the menstrual cycle. In other embodiments, the method may totally disregard the natural cycle.
- 20 The method is preferably multi-phased. The method may comprise administering for 10 to 12 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg; and further administering for 10 to 12 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg and drospirenone in amounts corresponding to daily doses ranging from 0.25 to 6 mg;
- 25 and further administering for 4 to 8 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.25 to 5 mg.

Similarly, the multi-phased method may comprise administering for 10 to 12 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from

30 0.1 to 5 mg; and further administering for 10 to 12 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg and drospirenone in amounts corresponding to daily doses ranging from 0.25 to 6 mg; and further administering for 4 to 8 days a daily dosage unit comprising of a placebo or blank.

24 139

A regimen of the method may comprise administering for at least 21 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg and drospirenone in amounts corresponding to daily doses ranging from 0.25 to 6 mg; and further administering for no more than 7 days a daily dosage unit comprising of a
5 placebo or blank. A similar regimen of method may comprise administering for at least 21 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg and drospirenone in amounts corresponding to daily doses ranging from 0.25 to 6 mg; and further administering for no more than 7 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from
10 0.1 to 5 mg.

Alternatively, a regimen of the method may comprise administering for at least 21 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg and drospirenone in amounts corresponding to daily doses ranging from
15 0.25 to 6 mg; and not administering a dosage unit for no more than 7 days.

An alternative embodiment of the method comprises administering for 21 to 28 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg and drospirenone in amounts corresponding to daily doses ranging from
20 0.25 to 6 mg.

The regimen may comprise of a continuous administration; that is to say that throughout the 21 to 28 days, a daily dose of estrogen is administered. Likewise, drospirenone may administered continuously, such that either one or both of estrogen and DRSP is/are
25 administered continuously.

In another embodiment, estrogen is administered continuously and drospirenone is administered sequentially. In such an embodiment, throughout the continuous administration of estrogen, DRSP is administered at regular intervals, for 1 to 20 days,
30 such as for 3 to 15 days, 5 to 14 days, particularly for 6 to 14 days. In another interesting embodiment of the regimen of the method, the estrogen dosage is lower for the 1 to 7 days immediately following said sequential administration of drospirenone.

Furthermore, in one embodiment of the invention, the method of treating and preventing
35 diseases, disorders and symptoms associated with deficient endogenous levels of

estrogen in women comprises continuous administration of estrogen and interrupted administration of progestin. Specifically the method may estrogen being administered continuously for 21 to 30 days and drospirenone being administered in a 3-day-on-3-day-off cycle. A particularly attractive embodiment within this alternative drospirenone being
5 administered on days 4 through 6, 10 through 12, 16 through 18, 22 through 24, and 28 through 30, whilst estrogen, such as estradiol is administered continuously.

The composition of the dosage unit may be formulated in any way conventional in the pharmaceutical art. In particular, as indicated above, the composition may be formulated
10 by a method comprising providing drospirenone and, if desired, an estrogen such as estradiol in micronized form in said unit dosage form, or sprayed from a solution onto particles of an inert carrier in admixture with one or more pharmaceutically acceptable excipients that promote dissolution of the drospirenone and an estrogen so as to promote rapid dissolution of drospirenone and preferably estradiol on oral administration.

15 Examples of suitable excipients include fillers, e.g. sugars such as lactose, glucose or sucrose, sugar alcohols such as mannitol, starch such as corn or potato starch or modified starch, lubricants such as talc or magnesium stearate and binders such as polyvinylpyrrolidone, cellulose derivatives, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose, or gelatin for making oral
20 dosage forms such as tablets, pills or capsules. Tablets may conveniently be coated with a suitable film-forming agent, e.g. hydroxypropylmethylcellulose. The present composition may also be formulated in liquid form, e.g. as solutions, suspensions or emulsions, together with conventional diluents or excipients in a manner known *per se* in the pharmaceutical art.

25

A particularly interesting regimen of a multi-phased pharmaceutical preparation comprises the sequential administration of both estrogen and drospirenone. An attractive embodiment of such as regimen will comprise a treatment free interval wherein no dosage unit is administered such as a comprising administering for 20 to 24 days a daily dosage
30 unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg, and drospirenone in amounts corresponding to daily doses ranging from 0.25 to 6 mg for the last 10 to 12 days of said 20 to 24 day, and not administering any dosage units for 4 to 8 days.

Alternatively, any interval wherein neither DRSP nor estrogen is administered, a placebo or blank is administered. Such a regimen of hormone replacement therapy can effectively comprise a method comprising administering for 20 to 24 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg, and further administering drospirenone in amounts corresponding to daily doses ranging from 0.25 to 6 mg for the last 10 to 12 days of said 20 to 24 day, and further administering for 4 to 8 days a daily dosage unit comprising no active ingredient.

An alternative regimen comprises administering for 20 to 24 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg, and further administering drospirenone in amounts corresponding to daily doses ranging from 0.25 to 6 mg for the last 10 to 12 days of said 20 to 24 day, followed by administering for 4 to 8 days a daily dosage of unit comprising estradiol in amounts less than daily dosage unit taken for said 20 to 24 day administration of estradiol.

In embodiments where the medicament is in the form of a number of separately packaged and individually removable dosage units placed in a packaging unit and intended for oral administration for a period of at least 21, such as at least 28 days and wherein the estrogen is estradiol, preferably at least 21 daily dosage units comprise a combination of estradiol in an amount from about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg; and 7 or less daily dosage units comprise estradiol in an amount from about 0.1 to 5 mg.

Alternatively, the medicament may be in the form of a number of separately packaged and individually removable dosage units placed in a packaging unit and intended for oral administration for a period of at least 28 days and at least 21 daily dosage units comprise a combination of estradiol in an amount from about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg and 7 or less daily dosage units comprise a blank or placebo.

It easily follows that the medicament may be in the form of a number of separately packaged and individually removable dosage units placed in a packaging unit and intended for oral administration for a period of at least 28 days and at least 21 daily dosage units comprise a combination of estradiol in an amount from about 0.1 to 5 mg

and drospirenone in an amount ranging from about 0.25 to 6 mg. There may not be any dosage units for the last 7 or less days of the regimen.

Patient compliance of the many embodiments of the regimen may be aided by means of a pharmaceutical preparation tailored to the patients needs or habits. One such preparation may consist of a number of separately packaged and individually removable daily dosage units placed into a packaging unit and intended for oral administration for a period of at least 21 days, such as at least 28 days, wherein said daily dosage units comprise a combination of estradiol in an amount ranging from about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg.

Furthermore, patient compliance may be aided by a regimen comprising a multi-phase pharmaceutical preparation.

Every regimen may be easily be adhered to by a multi-phased pharmaceutical preparation such as one consisting of a number of separately packaged and individually removable daily dosage units placed into a packaging unit and intended for oral administration for a period of 28 days wherein said daily dosage units comprise a combination of estradiol in an amount ranging from about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg. In such a preparation, the amount of active ingredient varies through the 28-day period.

An attractive embodiment relates to multi-phased pharmaceutical preparation consisting of a number of separately packaged and individually removable daily dosage units placed into a packaging unit and intended for oral administration for a period of 21 to 30 consecutive days wherein 10 to 15 said daily dosage units comprise a combination of estradiol in an amount ranging from about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg; and 10 to 15 said daily dosage units comprise estradiol in an amount ranging from about 0.1 to 5 mg. This embodiment is particularly suited for preparations wherein estrogen is administered continuously for 21 to 30 days and drospirenone is administered in a 3-day-on-3-day-off cycle. Preferably, within this embodiment, the preparation is designed so that drospirenone is administered on days 4 through 6, 10 through 12, 16 through 18, 22 through 24, and days 28 through 30.

Moreover, a multi-phased pharmaceutical preparation wherein the number of daily dosage units is 21 or 28, or a multiple of 21 or 28, such as 2 to 24, such as 2 to 12, particularly 2 to 8, such as multiples of 2 to 6.

- 5 Likewise, the invention relates to a method of treating diseases, disorders, and symptoms associated with estrogen deficiency comprising a multi-phased pharmaceutical preparation comprising daily dosage units which are administered for 1 to 12, preferably 2 to 8, such as 2, 3, 4 5, 6, 7, and 8 multiples of 28 days.
- 10 A packaging unit comprising the daily dosage units described above may be prepared in a manner analogous to that of making oral contraceptives or hormone replacement regimens. This may for instance be a conventional blister pack or any other form known for this purpose, for instance a pack comprising the appropriate number of dosage units (in this case at least 28, or for particular applications, a multiple of 28) in a sealed blister
- 15 pack with a cardboard, paperboard, foil or plastic backing and enclosed in a suitable cover. Each blister container may conveniently be numbered or otherwise marked.

- It is also envisaged that the present composition may be in the form of a parenteral formulation such as a subcutaneous implant or transdermal formulation. For making
- 20 implants, the active agents may suitably be formulated together with one or more polymers that are gradually eroded or degraded when in use, e.g. silicone polymers, ethylene vinylacetate, polyethylene or polypropylene.

- Where transdermal formulations are concerned, they may be prepared in the form of
- 25 matrices or membranes or as fluid or viscous formulations in oil or hydrogels. For transdermal patches, an adhesive which is compatible with the skin should be included, such as polyacrylate, a silicone adhesive or polyisobutylene, as well as a foil made of, e.g. polyethylene, polypropylene, ethylene vinylacetate, polyvinylchloride, polyvinylidene chloride or polyester, and a removable protective foil made from, e.g., polyester or paper
- 30 coated with silicone or a fluoropolymer. For the preparation of transdermal solutions or gels, water or organic solvents or mixtures thereof may be used. Transdermal gels may furthermore contain one or more suitable gelling agents or thickeners such as silicone, tragacanth, starch or starch derivatives, cellulose or cellulose derivatives or polyacrylic acids or derivatives thereof. Transdermal formulations may also suitably contain one or
- 35 more substances that enhance absorption through the skin, such as bile salts or

288
144

derivatives thereof and/or phospholipids. Suitable transdermal formulations may, for instance, be made in a manner analogous to that described in WO 94/04157 for 3-ketodesogestrel. Alternatively, transdermal formulations may be prepared according to a method disclosed in, e.g., BW Barry, "Dermatological Formulations, Percutaneous
5 Absorption", Marcel Dekker Inc., New York - Basel, 1983, or YW Chien, "Transdermal Controlled Systemic Medications", Marcel Dekker Inc., New York - Basel, 1987.

The present invention is further described in the following examples which are not in any way intended to limit the scope of the invention as claimed.

EXPERIMENTAL

Example 1

- 5 *Preparation of tablets containing drospirenone and estradiol may be performed in the following manner*

Tablet cores of the following composition

10	micronized drospirenone	3.00 mg
	micronized estradiol	1.00, 2.00, 3.00 mg
	lactose monohydrate	45.2, 46.2, 47.2 mg
	corn starch	14.40 mg
	modified starch	9.60 mg
15	polyvinylpyrrolidone 25,000	4.00 mg
	magnesium stearate	0.80 mg

are prepared by charging a fluidised bed granulator with 31.68 kg corn starch, 21.12 kg modified starch, 6.60 kg micronized drospirenone, 2.20, 4.40 or 6.6 kg of micronized
20 estradiol (for 1 mg, 2 mg, and 3 mg dose, respectively) and 99.44, 101.64, or 103.84 kg of lactose monohydrate (for 3 mg, 2 mg, and 1 mg dose, respectively) and activating the fluidised bed. An aqueous solution of 8.80 kg polyvinylpyrrolidone 25,000 in 46.20 kg purified water is sprayed continuously onto the fluidised bed while drying by heating the air stream of the fluidised bed. At the end of the process 1.76 kg magnesium stearate is
25 sucked into the granulator and mixed with the granules by maintaining the fluidised bed. The resulting granulate is pressed into tablet cores by compression using a rotary tablet press.

For tablets comprising 1 mg of estradiol, 2.22464 kg of hydroxypropylmethylcellulose and
30 0.44528 macrogol 6000 are dissolved in 14.67 kg purified water. 0.44528 kg talc, 1.25906 kg titanium dioxide and 0.02575 kg ferric oxide pigment are suspended in 10.26 kg purified water with stirring and homogenised. The solution and suspension are combined and used to coat the tablet cores by continuous application of the coating suspension in a coater. For tablets comprising 2 or 3 mg of estradiol, the specific weights of the reagents
35 for the preparation of the coating can easily be calculated.

81
146

An alternative formulation for the coatings of 1 mg tablets comprises 2.22464 kg of hydroxypropylmethylcellulose, 0.44528 kg of macrogol 600, 0.44528 kg of talc, 1.17326 of titanium dioxide, 0.07634 kg of ferric oxide pigment, yellow, and 0.03520 kg of ferric oxide pigment, red. A possible formulation for the coatings of 2 mg tablets comprises of
5 2.22464 kg of hydroxypropylmethylcellulose, 0.44528 kg of macrogol 600, 0.44528 kg of talc, 1.19636 of titanium dioxide and 0.08844 kg of ferric oxide pigment, red. A possible formulation for the coatings of 3 mg tablets comprises of 2.22464 kg of hydroxypropylmethylcellulose, 0.44528 kg of macrogol 600, 0.44528 kg of talc, 1.25906 of titanium dioxide and 0.02574 kg of ferric oxide pigment, red.

10

Example 2: Relative bioavailability

The evaluation of relative bioavailability of estradiol (E2) and drospirenone (DRSP), in an open randomised 2-way cross over study with volunteers. E2/DRSP after treatment with
15 either 2 mg of E2 + 2 mg of DRSP, 2 mg of E2 + 6 mg of DRSP coated tablets p.o versus 2 mg of E2 + 2 mg of DRSP oral solution.

Example 3: Repeated Dose

20 The evaluation of repeated dose pharmacokinetics (accumulation) and potential interaction between estradiol and drospirenone was performed. This open-label, randomised, intra-individual cross-over study of two dose level combinations with an intervening wash-out phase (4 weeks), and multiple application over 28 days was done with 4 dose combinations. A 4-week observation period was performed after the last dose.

25

Treatment A: 1 mg E2 + 1 mg DRSP, daily, p.o.

Treatment B: 1 mg E2 + 4 mg DRSP, daily, p.o.

Treatment C: 2 mg E2 + 1 mg DRSP, daily, p.o.

Treatment D: 2 mg E2 + 4 mg DRSP, daily, p.o.

30

Assessment: No statistically significant interaction was observed between the two active ingredients.

Example 4: Endometrial Protection

35

Primary Objective: To evaluate the efficacy of thirteen, 28 day cycles of continuous E2-DRSP combinations compared to continuous E2 by analysis of protection against hyperplasia in post-menopausal women.

- 5 Secondary Objectives: To evaluate the effect of endometrial morphology, bleeding patterns, metabolic and hemostatic laboratory parameters. Well-being of post-menopausal women as assessed by the Women's Health Questionnaire (WHQ) and The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36). Effect on the frequency and severity of hot flushes, and on the relief of urogenital symptoms. Drug
- 10 levels of DRSP and E2. Detailed evaluation of the metabolic parameters in subgroup.

Synopsis:

Dose Groups: E2 1 mg; E2 1 mg + DRSP 0.5 mg; E2 1 mg + DRSP 1 mg; E2 1 mg + DRSP 2 mg; E2 1 mg + DRSP 3 mg.

15

- Post-menopausal women with or without menopausal symptoms will be assigned 1 of 5 regimens. Endometrial effects will be evaluated by biopsy to determine the incidence of endometrial hyperplasia. Symptoms and bleeding patterns will be evaluated from subject diaries. General safety, and effects on specific biochemical and hematological
- 20 parameters will be evaluated. A post-menopausal quality of life assessment and evaluation of patient satisfaction will also be made.

Two-hour glucose tolerance tests, and 15-minute insulin tolerance tests were performed at certain sites.

25

Data Analysis

Endometrial biopsy at Visit 1 and Final Visit. Bleeding pattern information is recorded in a daily diary throughout the study.

- 30 Two analyses will be performed for the primary efficacy variable: i) 2-sided comparison of treatments and ii) 1-sided, within group interval estimation of dose effect.
- Frequency tables will be generated for visits at which endometrial biopsies are performed. These tables will display the number and percent of subjects in each endometrial response category for each treatment group (and by centre in case of a treatment-by-
- 35 centre interaction). Overall and between group comparison of the incidence of

hyperplasia among the treatment groups will be performed. This analysis will be intent-to-treat and will test the null hypothesis of no difference in response to treatments (unopposed vs. opposed estradiol) when adjusted for centre.

5 Interval estimation of dose response

The probability π_t will be estimated for each dose of DRSP (t 0.0, 0.5, 1.0, 2.0, 3.0).

Additionally, the upper limit of the one-sided 95% confidence interval will be calculated for each π_t separately. This means that the confidence intervals will be non-simultaneous.

10 **Example 5: Osteoporosis Prevention**

Primary Objective: Bone mineral density of the hip after 104 weeks of treatment.

Secondary Objectives: Bone mineral density (BMD) of the hip after 12, 28, 52, and 80 weeks of treatment. BMD of the lumbar spine, of the midshaft of the radius, of the total body. Effects on parameters for bone metabolism. Bleeding pattern. General safety.

The study will be performed as a double blind, placebo-controlled trial with 240 healthy, post-menopausal women randomly assigned to one of 4 groups of 60 after giving their informed consent.

The groups will be as follows:

- 1 mg E2 + 1 mg DRSP
- 1 mg E2 + 2 mg DRSP
- 1 mg E2 + 3 mg DRSP

25 Synopsis

Forty osteopenic patients (BMD hip T-score between -1 and -2.5) and 20 non-osteopenic patients should be enrolled in each group. All treatments will be applied daily *per os* during the whole treatment of 2 years without a treatment-free interval. In addition, the patients will be supplied with calcium tablets (500 mg of calcium daily). Measurements of bone mineral density of the hip will be measured on the left side utilising dual-energy x-ray absorptiometry at screening, baseline, and after 12, 28, 52, 80, and 104 weeks of treatment. Biochemical markers of bone remodelling will be measured at intervals.

84
149

Serum bone specific alkaline phosphatase, serum N-mid osteocalcin, urinary calcium/creatinine (second morning void), and urinary CrossLaps® /creatinine (second morning void) will additionally be evaluated.

5

Example 6: Menopausal Symptoms

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

10

Primary Objective: Hot flushes

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

15

Synopsis

Double-blind, placebo controlled trial with healthy, post-menopausal women randomly assigned to one of 4 groups

20

1 mg E2 + 1 mg DRSP

1 mg E2 + 2 mg DRSP

1 mg E2 + 3 mg DRSP

placebo

25 Synopsis:

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

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

30

Hot flushes 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 flushes 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,

35

urogenital symptoms. The intensity of the symptoms will be assessed as mild, moderate or severe.

- If the patient has an intact uterus, the occurrence of bleeding will be recorded every day
 5 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

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

10

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)

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
 15 change (C) in the number of hot flushes. C is defined as $(T-B) / B$, where T and B are individual means. T is the mean number of hot flushes per week, calculated by the observations during the weeks 3 through 16 of the treatment phase. B is the mean number of hot flushes per week, calculated from the observations of the 2-week pre-treatment phase.

20

Example 7: Lipid Profile

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
5 surrogate endpoint to estimate cardiovascular risk.

Primary Objectives: Lipid pattern including HDL cholesterol, LDL cholesterol

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

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

Groups:

1 mg E2 + 2 mg DRSP

1 mg E2 + 3 mg DRSP

20 Premique®/Premelle®: 0.625 mg conjugated estrogens + 5 mg MPA

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.

CLAIMS

1. A pharmaceutical composition comprising
- 5 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, $6\beta,7\beta;15\beta;16\beta$ -dimethylene-3-oxo- 17α -preg-4-ene-21,17-
- 10 carbolactone (drospirenone) in sufficient amounts to protect the endometrium from the adverse effects of estrogen,
- together with a pharmaceutically acceptable excipient or carrier.
- 15 2. A composition according to claim 1, wherein the deficient levels of estrogen are caused by natural menopause, peri-menopause, post-menopause, hypogonadism, castration or primary ovarian failure.
3. A composition according to any of claims 1 or 2, wherein the diseases, disorders and
- 20 symptoms are selected from the group comprising including hot flushes, sweating attacks, palpitations, sleep disorders, mood changes, nervousness, anxiety, poor memory, loss of confidence, loss of libido, poor concentration, diminished energy, diminished drive, irritability, urogenital atrophy, atrophy of the breasts, cardiovascular disease, changes in hair distribution, thickness of hair, changes in skin condition and osteoporosis.
- 25
4. A composition according to claim 3, wherein the diseases, disorders and symptoms are selected from the group comprising including hot flushes, sweating attacks, palpitations, sleep disorders, mood changes, nervousness, anxiety, urogenital atrophy, atrophy of the breasts and osteoporosis.
- 30
5. A composition according to claim 1, wherein the estrogen is selected from the group consisting of estradiol, estradiol sulfamates, estradiol valerate, estradiol benzoate, ethinyl estradiol, estrone, estriol, estriol succinate and conjugated estrogens, including conjugated equine estrogens such as estrone sulfate, 17β -estradiol sulfate, 17α -estradiol

88
153

sulfate, equilin sulfate, 17 β -dihydroequilin sulfate, 17 α -dihydroequilin sulfate, equilenin sulfate, 17 β -dihydroequilenin sulfate and 17 α -dihydroequilenin sulfate or mixtures thereof.

6. A composition according to claim 5, wherein the estrogen is selected from the group
5 consisting of estradiol, estradiol sulfamates, estradiol valerate, estradiol benzoate, estrone, and estrone sulfate or mixtures thereof.

7. A composition according to claim 6, wherein the estrogen is estradiol.

10 8. A composition according to claim 1, wherein drospirenone (DRSP) is in micronized form.

9. A composition according to any of claims 5 or 6, wherein at least one estrogen is in micronized form.

15

10. A composition according to claim 1, wherein the dose of DRSP corresponds to 15 to 70 mg per cycle, such as 20 to 60 mg per cycle, particularly 40 to 60 mg per cycle.

11. A composition according to claim 1, wherein the amount of DRSP corresponds to a
20 daily dose ranging from 0.25 to 10 mg, such as about 0.25 to 8, 0.25 to 6, 0.25 to 5, 0.5 to 4.5, 1 to 4, and 1.5 to 3.5 mg.

12. A composition according to claim 7, wherein the amount of estradiol corresponds to a daily dose ranging from 0.1 to 5 mg, such as about 0.2 to 4.5, 0.5 to 4, 1 to 3, in particular
25 1, 2, or 3 mg.

13. A pharmaceutical composition comprising
as a first active agent estradiol in amounts corresponding to a daily dose of 1 to 3 mg to treat diseases, disorders and symptoms associated with deficient endogenous levels of
30 estrogen in women,
and as a second active agent 6 β ,7 β ;15 β ;16 β -dimethylene-3-oxo-17 α -preg-4-ene-21,17-carbolactone (drospirenone) in amounts corresponding to a daily dose of 1 to 3.5 mg to protect the endometrium from the adverse effects of estrogen,
together with a pharmaceutically acceptable excipient or carrier.

35

14. Use of a combination of estrogen and drospirenone for the preparation of a medicament wherein the amount of estrogen is sufficient to treat diseases, disorders and symptoms associated with deficient endogenous levels of estrogen in women and the amount of drospirenone is sufficient to protect the endometrium from the adverse effects of estrogen.

15. The use according to claim 14, wherein the deficient levels of estrogen are caused by natural menopause, peri-menopause, post-menopause, hypogonadism, castration or primary ovarian failure.

10

16. The use according to claim 14, wherein the amount of estrogen is sufficient for the treatment of hot flushes, sweating attacks, palpitations, sleep disorders, mood changes, nervousness, anxiety, poor memory, loss of confidence, loss of libido, poor concentration, diminished energy, diminished drive, irritability, urogenital atrophy, atrophy of the breasts, cardiovascular disease, changes in hair distribution, thickness of hair, changes in skin condition or for the prevention or management of osteoporosis.

17. The use according to claims 16, wherein the amount of estrogen is sufficient for the treatment of hot flushes, sweating attacks, palpitations, sleep disorders, mood changes, nervousness, anxiety, urogenital atrophy, atrophy of the breasts or for the prevention or management of osteoporosis.

18. The use according to claim 14, wherein the estrogen is selected from the group consisting of estrogen is selected from the group consisting of estradiol, estradiol sulfamates, estradiol valerate, estradiol benzoate, ethinyl estradiol, estrone, estriol, estriol succinate and conjugated estrogens, including conjugated equine estrogens such as estrone sulfate, 17 β -estradiol sulfate, 17 α -estradiol sulfate, equilin sulfate, 17 β -dihydroequilin sulfate, 17 α -dihydroequilin sulfate, equilenin sulfate, 17 β -dihydroequilenin sulfate and 17 α -dihydroequilenin sulfate or mixtures thereof.

30

19. The use according to claim 18, wherein the estrogen is selected from the group consisting of estradiol, estradiol sulfamates, estradiol valerate, estradiol benzoate, estrone, and estrone sulfate or mixtures thereof.

35 20. The use according to claim 19, wherein the estrogen is estradiol.

21. The use according to claim 14, wherein drospirenone (DRSP) is in micronized form.
22. The use according to claim 14, wherein the estrogen is in micronized form.
- 5 23. The use according to claim 20, wherein the estradiol is in micronized form.
24. The use according to claim 14, wherein the dose of DRSP corresponds to 15 to 70 mg per cycle, such as 20 to 60 mg per cycle, particularly 40 to 60 mg per cycle.
- 10 25. The use according to claim 14, wherein the amount of DRSP corresponds to a daily dose ranging from 0.25 to 10 mg, such as about 0.25 to 8, 0.25 to 6, 0.25 to 5, 0.5 to 4.5, 1 to 4, and 1.5 to 3.5 mg.
26. The use according to claim 20, wherein the amount of estradiol corresponds to a daily
15 dose ranging from 0.1 to 5 mg, such as about 0.2 to 4.5, 0.5 to 4, 1 to 3, in particular 1, 2, or 3 mg.
27. The use according to claim 14, wherein the medicament is in the form a of a number of separately packaged and individually removable dosage units placed in a packaging
20 unit and intended for oral administration for a period of at least 28 days;
wherein at least 21 daily dosage units comprise a combination of estradiol in an amount from about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg; and 7 or less daily dosage units comprise estradiol in an amount from about 0.1 to 5 mg.
- 25 28. The use according to claim 14, wherein the medicament is in the form of a number of separately packaged and individually removable dosage units placed in a packaging unit and intended for oral administration for a period of at least 28 days;
wherein at least 21 daily dosage units comprise a combination of estradiol in an amount from about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg;
30 and 7 or less daily dosage units comprise a blank or placebo.
29. The use according to 14, wherein the medicament is in the form of a number of separately packaged and individually removable dosage units placed in a packaging unit and intended for oral administration for a period of at least 28 days,

- wherein at least 10 daily dosage units comprise estradiol in an amount from about 0.1 to 5 mg;
and at least 10 daily dosage unit comprise a combination of estradiol in an amount from about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg,
5 and 8 or less daily dosage units comprise a blank or placebo.

30. The use according to 14, wherein the medicament is in the form of a number of separately packaged and individually removable dosage units placed in a packaging unit and intended for oral administration for a period of at least 28 days;
10 wherein at least 10 daily dosage units comprise estradiol in an amount from about 0.1 to 5 mg,
and at least 10 daily dosage units comprise a combination of estradiol in an amount from about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg;
and 8 or less daily dosage units comprise estradiol in an amount from about 0.1 to 5 mg.
15

31. The use according to claim 14, wherein the medicament is in the form of a number of separately packaged and individually removable dosage units placed in a packaging unit and intended for oral administration for a period of at least 28 days;
wherein 28 daily dosage units comprising a combination of estradiol in an amount from
20 about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg.

32. A method of treating and preventing diseases, disorders and symptoms associated with deficient endogenous levels of estrogen in women comprising administering estrogen in sufficient amounts to alleviate said diseases, disorders and symptoms and
25 drospirenone in sufficient amounts to protect the endometrium from adverse effects of estrogen.

33. A method according to claim 32, wherein the deficient levels of estrogen are caused by natural menopause, peri-menopause, post-menopause, hypogonadism, castration or
30 primary ovarian failure.

34. A method according to claim 32, wherein the diseases, disorders and symptoms are selected from the group comprising including hot flushes, sweating attacks, palpitations, sleep disorders, mood changes, nervousness, anxiety, poor memory, loss of confidence,
35 loss of libido, poor concentration, diminished energy, diminished drive, irritability,

urogenital atrophy, atrophy of the breasts, cardiovascular disease, changes in hair distribution, thickness of hair, changes in skin condition or for the prevention or management of osteoporosis.

- 5 35. A method according to claim 34, wherein the diseases, disorders and symptoms are selected from the group comprising including hot flushes, sweating attacks, palpitations, sleep disorders, mood changes, nervousness, anxiety, urogenital atrophy, atrophy of the breasts or for the prevention or management of osteoporosis.
- 10 36. A method according to claim 32, wherein the estrogen is selected from the group consisting of estrogen is selected from the group consisting of estradiol, estradiol sulfamates, estradiol valerate, estradiol benzoate, ethinyl estradiol, estrone, estriol, estriol succinate and conjugated estrogens, including conjugated equine estrogens such as estrone sulfate, 17 β -estradiol sulfate, 17 α -estradiol sulfate, equilin sulfate, 17 β -
- 15 dihydroequilin sulfate, 17 α -dihydroequilin sulfate, equilenin sulfate, 17 β -dihydroequilenin sulfate and 17 α -dihydroequilenin sulfate or mixtures thereof.
37. A method according to claim 36, wherein the estrogen is selected from the group consisting of estradiol, estradiol sulfamates, estradiol valerate, estradiol benzoate,
- 20 estrone, and estrone sulfate or mixtures thereof.
38. A method according to claim 37, wherein the estrogen is estradiol.
39. A method according to claim 32, wherein drospirenone (DRSP) is in micronized form.
- 25 40. A method according to claim 32, wherein the estrogen is in micronized form.
41. A method according to claim 38, wherein the estradiol is in micronized form.
- 30 42. A method according to claim 32, wherein the dose of DRSP corresponds to 15 to 70 mg per cycle, such as 20 to 60 mg per cycle, particularly 40 to 60 mg per cycle.
43. A method according to claim 32, wherein the amount of DRSP corresponds to a daily dose ranging from 0.25 to 10 mg, such as about 0.25 to 8, 0.25 to 6, 0.25 to 5, 0.5 to 4.5,
- 35 1 to 4, and 1.5 to 3.5 mg.

44. A method according to claim 38, wherein the amount of estradiol corresponds to a daily dose ranging from 0.1 to 5 mg, such as about 0.2 to 4.5, 0.5 to 4, 1 to 3, in particular 1, 2 or 3 mg.
- 5 45. A method of treating and preventing diseases, disorders and symptoms associated with deficient endogenous levels of estrogen in women comprising administering estradiol in amounts corresponding to daily doses of 1 to 3 mg and drospirenone in amounts corresponding to daily doses of 1 to 3.5 mg.
- 10 46. A method according claim 32, comprising administering for 10 to 12 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg; and administering for 10 to 12 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg and drospirenone in amounts
15 corresponding to daily doses ranging from 0.25 to 6 mg; and administering for 4 to 8 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.25 to 5 mg.
47. A method according to claim 32, comprising
20 administering for 10 to 12 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg; and administering for 10 to 12 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg and drospirenone in amounts corresponding to daily doses ranging from 0.25 to 6 mg; and
25 administering for 4 to 8 days a daily dosage unit comprising of a placebo or blank.
48. A method according to claim 32, comprising administering for at least 21 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg and drospirenone in amounts
30 corresponding to daily doses ranging from 0.25 to 6 mg; and administering for no more than 7 days a daily dosage unit comprising of a placebo or blank.
49. A method according to claim 32, comprising

administering for at least 21 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg and drospirenone in amounts corresponding to daily doses ranging from 0.25 to 6 mg; and administering for no more than 7 days a daily dosage unit comprising estradiol in amounts
5 corresponding to daily doses ranging from 0.1 to 5 mg.

50. A method according to claim 32, comprising administering for 21 to 28 days a daily dosage unit comprising estradiol in amounts corresponding to daily doses ranging from 0.1 to 5 mg and drospirenone in amounts
10 corresponding to daily doses ranging from 0.25 to 6 mg.

51. A method according to any of claims 32 to 45, wherein the estrogen is administered continuously.

15 52. A method according to any of claims 32 to 45, wherein the estrogen and drospirenone are administered continuously.

53. A method according to any of claims 32 to 45, wherein the estrogen is administered continuously and drospirenone is administered sequentially.
20

54. A method according to claim 53, wherein the estrogen dosage is lower for the 1 to 7 days immediately following said sequential administration of drospirenone.

55. A method according to claim 32, wherein estrogen is administered continuously and
25 drospirenone is administered in an interrupted manner.

56. A method according to claim 55, wherein estrogen is administered continuously for 21 to 30 days and drospirenone is administered in a 3-day-on-3-day-off cycle.

30 57. A method according to claim 56, wherein drospirenone is administered on days 4 through 6, 10 through 12, 16 through 18, 22 through 24, and 28 through 30.

58. A method according to any of claims 32 to 45, wherein the estrogen and the drospirenone are each administered sequentially with a treatment-free interval.

59. A method according to claim 32, comprising
administering for 20 to 24 days a daily dosage unit comprising estradiol in amounts
corresponding to daily doses ranging from 0.1 to 5 mg,
and drospirenone in amounts corresponding to daily doses ranging from 0.25 to 6 mg for
5 the last 10 to 12 days of said 20 to 24 days, and
administering for 4 to 8 days a daily dosage unit comprising no active ingredient.

60. A method according to claim 32, comprising
administering for 20 to 24 days a daily dosage unit comprising estradiol in amounts
10 corresponding to daily doses ranging from 0.1 to 5 mg, and drospirenone in amounts
corresponding to daily doses ranging from 0.25 to 6 mg for the last 10 to 12 days of said
20 to 24 day, and
administering for 4 to 8 days a daily dosage of unit comprising estradiol in amounts less
than daily dosage unit taken for said 20 to 24 day administration of estradiol.

15

61. A method according to claim 32, comprising
administering for 20 to 24 days a daily dosage unit comprising estradiol in amounts
corresponding to daily doses ranging from 0.1 to 5 mg,
and drospirenone in amounts corresponding to daily doses ranging from 0.25 to 6 mg for
20 the last 10 to 12 days of said 20 to 24 day, and
not administering any dosage units for 4 to 8 days.

62. A method according to any of claims 32 to 61, wherein the estrogen and/or
drospirenone are administered in oral formulation, from a patch, from an implant or
25 combinations thereof.

63. A method according to claim 62, wherein the estrogen and/or drospirenone are
administered in oral formulation.

30 64. A method according to any of claims 46 to 61, wherein the daily dosage units are
administered for 1 to 12, preferably 2 to 8, such as 2, 3, 4 5, 6, 7, and 8 multiples of 28
days.

65. A multi-phased pharmaceutical preparation consisting of a number of separately
35 packaged and individually removable daily dosage units placed into a packaging unit and

intended for oral administration for a period of at least 21 days wherein said daily dosage units comprise a combination of estradiol in an amount ranging from about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg.

- 5 66. A multi-phased pharmaceutical preparation consisting of a number of separately packaged and individually removable daily dosage units placed into a packaging unit and intended for oral administration for a period of 28 days wherein said daily dosage units comprise a combination of estradiol in an amount ranging from about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg.

10

67. A multi-phased pharmaceutical preparation consisting of a number of separately packaged and individually removable daily dosage units placed into a packaging unit and intended for oral administration for a period of 28 days, wherein at least 21 said daily dosage units comprise a combination of estradiol in an amount ranging from about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg; and
15 no more than 7 said dosage units comprise a placebo or a blank.

68. A multi-phased pharmaceutical preparation consisting of a number of separately packaged and individually removable daily dosage units placed into a packaging unit and intended for oral administration for a period of 28 days, wherein at least 21 said daily dosage units comprise a combination of estradiol in an amount ranging from about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg; and
20 no more than 7 said dosage units comprise estradiol in an amount ranging from about 0.1 to 5 mg.

69. A multi-phased pharmaceutical preparation consisting of a number of separately packaged and individually removable daily dosage units placed into a packaging unit and intended for oral administration for a period of at least 28 consecutive days, wherein at least 10 said daily dosage units comprise estradiol in an amount ranging from about 0.1 to 5 mg; and
30 at least 10 said daily dosage units comprises a combination of estradiol in an amount ranging from about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg; and
35 6 mg; and

no more than 8 of said daily dosage units comprise a placebo or blank.

70. A multi-phased pharmaceutical preparation consisting of a number of separately packaged and individually removable daily dosage units placed into a packaging unit and
5 intended for oral administration for a period of at least 28 consecutive days, wherein at least 10 said daily dosage units comprise estradiol in an amount ranging from about 0.1 to 5 mg; and
at least 10 said daily dosage units comprises a combination of estradiol in an amount ranging from about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to
10 6 mg; and
no more than 8 of said daily dosage units comprise estradiol in an amount ranging from about 0.1 to 5 mg.

71. A multi-phased pharmaceutical preparation consisting of a number of separately
15 packaged and individually removable daily dosage units placed into a packaging unit and intended for oral administration for a period of 21 to 30 consecutive days, wherein 10 to 15 said daily dosage units comprise a combination of estradiol in an amount ranging from about 0.1 to 5 mg and drospirenone in an amount ranging from about 0.25 to 6 mg; and
20 10 to 15 said daily dosage units comprise estradiol in an amount ranging from about 0.1 to 5 mg.

72. A preparation according to any of claims 65 to 71, wherein the number of daily dosage units is at least 21 or a multiple of 21 such as 2 to 12, particularly 2 to 8, such as 2 to 6.
25

73. A preparation according to any of claims 65 to 71, wherein the number of daily dosage units is 28 or a multiple of 28 such as 2 to 12, particularly 2 to 8 such as 2 to 6.

74. A preparation according to any of claims 65 to 71, wherein said daily dosage units
30 comprise estradiol and/or drospirenone in micronized form or sprayed from a solution onto particles of inert carrier.

75. A use of an estrogen (and/or naturally or synthetic derivative thereof) in sufficient amounts for the treatment of menopausal and post-menopausal symptoms and the
35 prevention of osteoporosis in menopausal and post-menopausal women

9#
162

and 6 β ,7 β ;15 β ;16 β -dimethylene-3-oxo-17 α -preg-4-ene-21,17-carbolactone (drospirenone) in sufficient amounts to protect the endometrium from the adverse effects of estrogen for the manufacture of a medicament.

- 5 76. A use of an estrogen (and/or naturally or synthetic derivative thereof) in sufficient amounts for the treatment of menopausal and post-menopausal symptoms and the prevention of osteoporosis in menopausal and post-menopausal women and 6 β ,7 β ;15 β ;16 β -dimethylene-3-oxo-17 α -preg-4-ene-21,17-carbolactone (drospirenone) in sufficient amounts to protect the endometrium from the adverse effects of estrogen
- 10 for the manufacture of a medicament for hormone replacement therapy.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 01/00041

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/585 A61P5/30

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 07081 A (SATURNUS) 16 March 1995 (1995-03-16) cited in the application claims 1,6,7 page 1, line 1-6 --- -/--	1,2,5-7, 10-15, 18-20, 24-26, 32,33, 36-38, 42-45, 51-53, 62,63, 75,76

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

25 April 2001

Date of mailing of the international search report

07/05/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Peeters, J

100
165

INTERNATIONAL SEARCH REPORT

In International Application No
PCT/IB 01/00041

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 27929 A (SCHERING) 2 July 1998 (1998-07-02) claims 1-11,13 page 3, paragraph 2 page 6, line 27-35 -----	1,2,5-7, 10-15, 18-20, 24-28, 32,33, 36-38, 42-45, 48, 51-53, 62-65, 75,76

INTERNATIONAL SEARCH REPORT

Information on patent family members

In International Application No

PCT/IB 01/00041

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9507081 A	16-03-1995	NL 9301562 A	03-04-1995
		AU 1848899 A	29-04-1999
		AU 708881 B	12-08-1999
		AU 7695294 A	27-03-1995
		CA 2171460 A	16-03-1995
		CN 1133011 A	09-10-1996
		EP 0717626 A	26-06-1996
		FI 961098 A	03-04-1996
		HU 74452 A	30-12-1996
		JP 9502194 T	04-03-1997
		US 5827843 A	27-10-1998
WO 9827929 A	02-07-1998	DE 19654609 A	25-06-1998
		AU 5981098 A	17-07-1998

101
166