

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

Número del expediente 04-117322

Solicitante SCHERING AKTIENGESELLSCHAFT

SOLICITUD
PÚBLICA

Apoderado GUSTAVO HOLLMANN RESTREPO

Título de la nueva creación o denominación del signo: TRATAMIENTO DE
HIPERTENSIÓN EN MUJERES QUE RECIBEN TERAPIA DE REEMPLAZO HORMONAL

Gaceta 562

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE

Nombre PROCAPS S.A

Dirección CALLE 80 No. 78b-201

Nacionalidad o Domicilio COLOMBIA
Lugar de Constitución BARRANQUILLA

Teléfono 371 99 00 Fax 373 08 18
E-mail

IDENTIFICACIÓN

C.C. ☐ NIT ☒

C.E. ☐ Otro ☐

Cual

Número 802.006 279-4

REPRESENTANTE
O APODERADO

Nombre REINALDO PINILLA
MORENO

Dirección TRANSVERSAL 13 A #119-95

Teléfono OFICINA 104 Fax
E-mail 2131213 6121979
negocios@optimum-co.com

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual

Número 80425609 TP 91563

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
revelado, 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. REINALDO PINILLA MORENO

FIRMA. [Firma manuscrita]

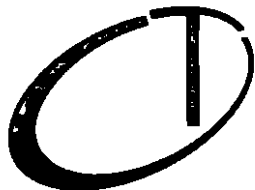
C.C 80425609

TP 91563 CSJ

NOTARIA SEXTA DE BOGOTÁ
RECONOCIMIENTO Y PRESENTACION PERSONAL
Bogotá, D.C. **28 JUN 2006**
Ante mí **PABLO MENDEZ BARAJAS**
NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTÁ
Comparecieron _____
_____ quien (as) exhibió(eron) la(s) C.C. _____
y declaró(aron) que la(s) firma(s) que aparece(n) en el presente documento es(son) la(s) suya (s) y que el contenido del mismo es cierto. En constancia se firma esta diligencia.

[Firma manuscrita]





ptimum

163 3
Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 04 117.322

Asunto : Oposición a la solicitud de patente de Invención titulada
"TRATAMIENTO DE LA HIPERTENSIÓN EN MUJERES
QUE RECIBEN TERAPIA DE REEMPLAZO
HORMONAL".

Solicitante : SCHERING AKTIENGESELLSCHAFT.

Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 562 del 31 de Marzo de 2006

Yo, **REINALDO PINILLA MORENO**, abogado con tarjeta profesional N° 91563 del consejo superior de la judicatura, en mi condición de apoderado 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 y por orden expresa de mi representada, presento oposición a la concesión del registro de la patente de Invención titulada **"TRATAMIENTO DE LA HIPERTENSIÓN EN MUJERES QUE RECIBEN TERAPIA DE REEMPLAZO HORMONAL"**, solicitada por **SCHERING AKTIENGESELLSCHAFT.**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

Transversal 13ª N° 119-95, Of. 104 Tel (571) 2 13 12 13 - 6 20 50 21 - Fax (571) 6 12 19 79

E-mail: negocios@optimum-co.com - www.optimum-co.com

Bogotá Colombia

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 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 23 de noviembre de 2004, reivindicando prioridad bajo US 60/375.439 del 26/04/2002 y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 562 del 31 de Marzo de 2006, página 469, N° publicación 1357, cuya publicación internacional corresponde a la WO03090755 del 2003-11-06.

2.2. La solicitud colombiana 04 117.322 objeto de la presente oposición, se refiere a un método para reducir la tensión arterial y lograr el efecto de terapia de reemplazo hormonal (TRH) en una paciente hembra humana hipertensa, que comprende

administrar a dicha paciente drospirenona (DRSP) en dosis de 0,5-3 mg/día y 17 β -estradiol en dosis de 1-3 mg/día; donde además la administración de medicación antihipertensiva a dicha paciente; en el cual dicha paciente comenzó a tomar la medicación antihipertensiva antes de iniciarse la administración de dicha DRSP y dicho 17 β -estradiol; en el cual dicha medicación antihipertensiva se administra conjuntamente con la administración de dicha DRSP y dicho 17 β -estradiol; en el cual la administración de dicha medicación antihipertensiva se inicia después de iniciarse la administración de dicha DRSP y dicho 17 β -estradiol; en el cual dicha medicación antihipertensiva es un diurético, un bloqueante α -adrenérgico, un bloqueante β -adrenérgico, un agente que actúa sobre el SNC, un bloqueante neuronal adrenérgico, un vasodilatador, un inhibidor de la enzima convertidora de la angiotensina I (ECA), un bloqueante del canal del calcio, un inhibidor de la renina o una combinación de los mismos.



2.3. En primera instancia, se debe advertir que las reivindicaciones se refieren a un método terapéutico y según la legislación, decisión 486 de la Comunidad Andina de Naciones, 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"*. Sólo serán patentables los productos o procedimientos. Por lo tanto la presente solicitud objeto de oposición no puede ser objeto de patentabilidad.

2.1. De otra parte 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

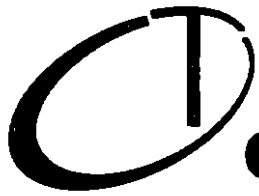
1668

objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentre el siguiente documento que afecta su patentabilidad respecto a la novedad:

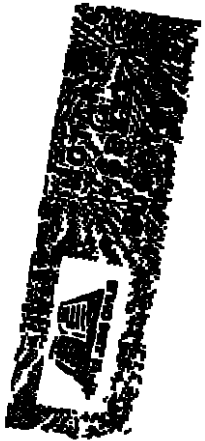
- D1: WO0152857, 2001-07-26.

2.2. Ahora bien, el documento D1, particularmente en la descripción y reivindicaciones, se refiere a un método para bajar la tensión arterial y efectuar una terapia de reemplazo hormonal (HRT) en una mujer que sufre de hipertensión, que comprende administrar cantidades eficaces de drospirenona y un estrógeno. Según este documento anterior, se revela una composición farmacéutica en forma de una forma de dosificación oral, que comprende: i) un estrógeno, con la excepción de etinilestradiol; ii) drospirenona, en una cantidad que corresponde a una dosis diaria que oscila de 0, 25 a 10 mg; y iii) un excipiente o vehículo farmacéuticamente aceptable, en la que dicha drospirenona está en una forma que tiene una superficie específica mayor que 10.000 cm²/g. Según este documento D1, se revela el uso de una composición que comprende un estrógeno tal como estradiol y drospirenona para una terapia de reemplazo de hormonas. En tales revelaciones anteriores según la página 9 segundo párrafo del documento anterior D1, se afirma que las dosis del compuesto corresponden a dosis definidas y es especialmente usado donde la mujer sufre de otros desórdenes o trastornos no compatibles con el empleo de una fuente exógena de estrógeno como la hipertensión. Igualmente, se afirma que la dosis de drospirenona puede ser tal que el trastorno, la enfermedad o el síntoma son aliviados. Por lo tanto, el presente documento no revela una composición nueva en comparación con este documento D1.





16x7

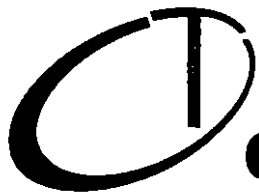


2.3. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 04 117.322 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

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

2.4.1. **CARECE DE NOVEDAD:** Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."* A la fecha de prioridad, 26 de abril de 2004, ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1, un método para reducir la tensión arterial y lograr el efecto de terapia de reemplazo hormonal (TRH) en una paciente hembra humana hipertensa, sobre el cual busca protección en el capítulo reivindicatorio.

2.4.2. **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 este no es aplicable industrialmente porque primero no se obtiene



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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 métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

2.5. 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 Paises 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 los dos de los tres requisitos de patentabilidad.

2.6. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada ***"TRATAMIENTO DE LA HIPERTENSIÓN EN MUJERES QUE RECIBEN TERAPIA DE REEMPLAZO HORMONAL"***, solicitada por ***SCHERING AKTIENGESELLSCHAFT***, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 562.

3. PRUEBAS

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

- D1: WO0152857, 2001-07-26.



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:

- D1: WO0152857, 2001-07-26.

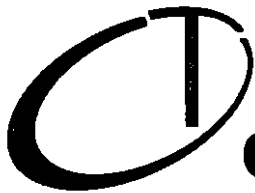
6. NOTIFICACIONES

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 Transversal 13ª N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,

C.C. 80425.685

Transversal 13ª N° 119-95, Of. 104 Tel (571) 2 13 12 13 - 6 20 50 21 - Fax (571) 6 12 19 79
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia



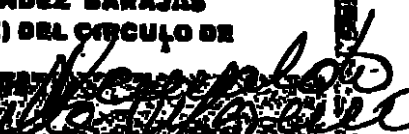
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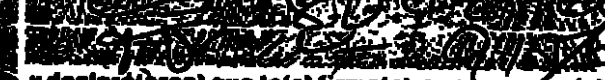
18
120
Derecho de la Competencia, Propiedad Industrial y Comercio Exterior


REINALDO PINILLA MORENO

C.C. 80'425.609 de Bogotá

T.P.A. 91563 del C.S. de la J.

NOTARIA SEXTA DE BOGOTÁ
RECONOCIMIENTO Y PRESENTACION PERSONAL
Bogotá, D.C. **28 JUN 2006**
Ante mí **PABLO MENDEZ BARRAJAS**
NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTÁ
Comparecieron: 

quien (as) exhibió(aron) la(s) C. C. 
y declaró(aron) que la(s) firma(s) que aparece(n)
en el presente documento es(son) la(s) cuya (s) y
que el contenido del mismo es cierto. En constan-
cia se firma esta diligencia. ..



RESPONSABLE : _____

121

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

ESTA CERTIFICACION DE EXCEDENTE DE PAGO, SOLO PODRA SER UTILIZADA
RECIBO OFICIAL DE CAJA No. 19302
PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER
FECHA JUNIO 28 DE 2006
SUSTITUIDA POR NINGUN RECIBO.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 04-117322- -00004-0000
Dec. 2006-06-26 16:38:07 Dep. 2020 N.J.E.C.-E-ACIONES
Tit. " PATENTE" II
Cif. 379 FASE NACIONAL II
IN 100 OBSERVACIONES EN LA

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PBO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO POPULAR	050-00110-6	37898012	05/05/2006	521,000.00
GYNOFARM S.A.	CONSIGNACION	BANCO POPULAR	050-00110-6	52569398	02/06/2006	246,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
		12 MARCAS Y LEMAS COMERCIALES	246,000.00
		TOTAL :	\$ 246,000.00

SON: DOSCIENTOS CUARENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____



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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 **REINALDO PINILLA MORENO**, abogado titulado, identificado como aparece al pie de su firma, con tarjeta profesional No. 91563 expedida por el Consejo Superior de la Judicatura, poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 04.117.322, de título: **"TRATAMIENTO DE LA HIPERTENSIÓN EN MUJERES QUE RECIBEN TERAPIA DE REEMPLAZO HORMONAL"**, publicada en la gaceta No. 562 del 31 de Marzo de 2006.

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 31 días del mes de Mayo de 2006.


PROCAPS S.A.
WALTER TANAKA TATEKAWA
C.C. N° 16.251.923 de Palmira
Representante Legal

Acepto,


REINALDO PINILLA MORENO
C.C. 80'425.609 de Bogotá
T.P.A. 91563 del C.S. de la J.

SECCION NOTARIA DEL CIRCULO DE BARRANQUILLA

ADY ISABEL NAMEN SEGURA

NOTARIA SECCION DEL CIRCULO DE BARRANQUILLA

OLIGRAFIA DE PRESENTACION PERSONAL Y RECONOCIMIENTO

Yo, la suscrita Notaria Certifico que este escrito fue
presentado Personalmente por NATHER
TANAKA TOTEKAWA

Identificación: 16251923

Especialidad: Notario

Quien declara que el contenido es cierto y que la
firma puesta en él es suya.

Firma: [Firma]

Huella del Comprobatario

05 JUN 1998

REPUBLICA DE COLOMBIA

NOTARIA SECCION DEL CIRCULO DE BARRANQUILLA

[Firma]



***** 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
04*****

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,

C E R T I F I C A

Que por Escritura Pública No. 1.190 del 22 de Julio de 1976, ot rgada 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, ot rgada 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, ot rgada 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, torgada 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 E R T I F I C A

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

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

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

Que por Escritura Pública No. 3.615 del 06 de Dic/bre de 1996, tr gada 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-----
cambi 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, tr gada 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-----
cambi 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/ 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.

DOMICILIO PRINCIPAL: Barranquilla.

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

PROCAPS S.A.-----

NIT: 890.106.527-5.

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, así como la comercializacion interna y externa de los productos terminados, d) La compra, venta, importación, exportación y distribución de toda clase de elementos instrumentales y equipos medicos, quirurgicos, odontologicos, y hospitalarios para la salud humana y animal. e) La compra, venta, exportación y distribución 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 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 asesoría 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., así como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal industrial; h)-Adquirir, operar, administrar y explotar, a cualquier

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NIT: 890.106.527-5.

titul , 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, s ci o fundador de empresas que tengan igual o similar objeto, comprar, vender, importar y exportar maquinarias, insumos y repuest s 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 t do tipo de actos y contratos necesarios para desarrollar sus operaci - nes; girar, aceptar, otorgar y protestar todo tipo de titulos val - res e instrumentos negociables; comprar, vender y constituir gravamenes sobre bienes muebles e inmuebles; designar representantes 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 s ci s, 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
Aut rizado		
\$*****2.000.000.000	*****2.000.000	*****1.000
Suscrito		
\$*****1.220.000.000	*****1.220.000	*****1.000
Pagado		
\$*****1.220.000.000	*****1.220.000	*****1.000

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad c rrespondera 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 tras: Autorizar cualquier acto o contrato cuya cuantia sea superi r 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 soci s, se requerira que la operacion sea aprobada con el vot de por l menos 2/3 partes de los integrantes de la Junta Directiva. La s ciedad tendra un Presidente , quien ejercera la representa - ci n legal de la sociedad y tendra las siguientes atribu - ci nes entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. Ejercer la Representaci n Legal de la sociedad en todos los actos y contratos que se requieran para el desarroll del bjeto s cial, de c nf rmidad con lo previsto en las leyes y en los presentes estatutos. C nstituir apoderados judiciales y extrajudiciales, recibir notificaci nes,

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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 cuantía sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dólares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el día en que se surta la transacción o celebración del acto. Las demás funciones que le correspondan como Representante Legal por disposición de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendrá un suplente, designado por la Junta Directiva, quien reemplazará al Presidente en sus faltas temporales, absolutas o meramente accidentales, con idénticas facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendrá un Vicepresidente designado por la Junta Directiva, quien también ejercerá la representación legal de la sociedad, pudiendo ejercerla conjunta separadamente con el Presidente. El vicepresidente tendrá 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 representación 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 cuantía sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dólares de los Estados Unidos de America (US\$150.000), liquidados a la tasa de cambio representativa del mercado vigente el día en que se surta la aprobación o celebración 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 interés 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 demás funciones que le corresponda como Representante legal por disposición de la ley, de estos estatutos o de la Junta Directiva. El Vicepresidente tendrá (1) suplente, designado por la Junta Directiva, quien lo reemplazará conjunta separadamente en sus faltas temporales, absolutas o meramente accidentales, con idénticas facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendrá un (1) Gerente General, con su respectivo Suplente, designados por la Junta Directiva. El Suplente reemplazará al Gerente General, en sus faltas

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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 cambi 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 partes de interes, inversiones y todo tipo de derechos de la sociedad 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 S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio,

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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 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
Revis r Fiscal Ppal. Vargas Pertuz Ana Isabel	CC.*****32.696.645

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

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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 publica No. 2.608 del 5 de Octubre del 2.001, registrada en la Notaria 2a. de Barranquilla, inscrita en esta Camara de Comercio el 8 de Noviembre del 2.001, bajo los Nos. 95.771, 2.056, 2.057, 2.058, 2.059, 2.060, 2.061, 2.062 y 2.064 del libro respectivo, se reforma totalmente el articulo 65, contenido en la escritura publica No. 3.705 de Noviembre 6 de 1.998, de la Notaria Segunda del Circuito de Barranquilla, y se constituyen los siguientes Apoderados Generales, quienes tendran las funciones que a continuaci n se indican en razon de su cargo en la sociedad: 1.-Se c nfiere Poder Especial, Amplio y Suficiente a los senores: WALTER TANAKA TATEKAWA, C.C. No. 16.251.923; WILLIAM ALBERTO BARROS CERRA, C.C. No. 8.715.941, para que cada uno en forma independiente en nombre y representacion de PROCAPS S.A., suscriba todas las declaraciones tributarias, aduaneras y cambiarias a que este obligada la sociedad, asi como para que responda todo tipo de requerimiento s -licitudes de informacion de las autoridades tributarias, aduaneras cambiarias, en los ordenes Distrital, Departamental y Nacional. 2.-Se c nfiere Poder Especial, amplio y suficiente, a los siguientes senores que conforman el Grupo A y el Grupo B para que conjuntamente suscriban contratos de suministros de mercancías y servicios con entidades oficiales, hasta por la suma de US\$800.000.00 (OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA), liquidados a la tasa representativa del mercado vigente en el día que se realice la respectiva transaccion. GUPO A: GUILLERMO LUIS URIBE OCHO C.C. No. 70.073.754, LINO LAZALA SILVA VARGAS C.C. No. 19.260.410, JAIRO MOLINA MEJIA C.C. No. 8.706.380, CLAUDIA TANGARIFE CASTILLO C.C. No. 41.660.-293. BRUPO B: WALTER TANAKA TATEKAWA C.C. No. 16.251.923, HENRY CARO DIAZ C.C. No. 19.395.298, CARMEN ALICIA FLOREZ C.C. No. 22.434.044, CARMEN ALICIA HERRERA DIAZGRANADOS C.C. No. 22.377.540. Para el ejercicio de estas facultades se requiera por lo menos la firma de uno (1) de los apoderados especiales del Grupo A y uno de los apoderados especiales del Grupo B; 3.-Se otorga Poder General, Amplio y Suficiente a la Doctora JOSEFINA MIELES BUELVAS C.C. No. 33.138.497, a la Doctora MARCELA CARVAJALINO PAGANO C.C. No. 22.579.748, y al Doctor DANIEL MORENO VILLALBA, C.C. No. 19.113.210; para que cada uno representen a PROCAPS S.A., ante todo tipo de autoridades administrativas y judiciales, en asuntos de naturaleza cambiaria y fiscal, tales como: Contestar e interponer demandas y requerimientos, comparecer en juicios, pedir la practica de pruebas, recibir notificaciones, interponer recursos y ejercer acciones contenciosas administrati-

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vas y de tutela, transigir, conciliar, recibir en nombre de la sociedad desistir, sustituir y reasumir este mandato. Para la celebraci n de cualquier acuerdo conciliatorio o transaccional, judicial ex-
trajudicial, cualquiera que sea su cuantia, los Apoderados deberan aportar la autorizacion escrita del Representante Legal de la socie-
dad. Los Apoderados podran presentar solicitudes de devolucion y/o compensacion de impuestos y recibir los pagos por devoluciones de impuestos, firmar, notificarse y realizar todo acto necesario para cumplir con el mandato encomendado.-----

C E R T I F I C A

Que segun documento privado de fecha 7 de junio de 2000, inscrit en esta Camara de Comercio el 8 de junio de 2000, bajo el No.1.786 del libro respectivo, consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982 de Barranquilla, actuando como Presidente y Representante Legal de la sociedad PROCAPS S.A, confiere poder especial, amplio y suficiente a KAREN FIGUEROA GARCIA, C.C.No.32.732.070 de Barran-
quilla, para que en su nombre y representacion de la sociedad sus-criba todas declaraciones cambiarias a que este obligada PROCAPS S.A, en el giro normal de sus negocios y operaciones sociales.--

C E R T I F I C A

Que segun Documento Privado del 13 de diciembre del 2.002, inscrito en esta Camara de Comercio el 15 de enero del 2.003 bajo el No.2.290 del libro respectivo, el senor RUBEN MINSKI GONTOVNIK, C.C.No.7.463.982, en calidad de REPRESENTANTE LEGAL, y en condicion de PRESIDENTE de PROCAPS S.A., mediante el presente documento otorgo PODER ESPE-
CIAL al Sr. MARLON TATIS PAREDES, C.C.No.72.176.874, para que en representacion de PROCAPS S.A., suscriba declaraciones, reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exteri r y/
cualquier entidad del Estado que haga sus veces. En consecuencia, el Sr. MARLON TATIS PAREDES, podra suscribir en representaci n de PROCAPS S.A. declaraciones, reportes y cualquier tipo de document s relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces.-----

C E R T I F I C A

Que segun documento privado del 10 de noviembre del 2004, inscrito en esta Camara de Comercio el 1 de diciembre del 2.004, baj el No. 2.753 del libro respectivo consta que RUBEN MINSNSKI GONTOVNIK, C.C.

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7.463.982 de Barranquilla, actuando como Presidente y Representante Legal de la sociedad PROCAPS S.A, confiere poder especial, amplio y suficiente a ANTONIO VARELA DIAZ, C.C.No.72.004.669 de Barranquilla, para que en nombre y representacion de la sociedad firme las declaraciones cambiarias a que este obligada PROCAPS S.A., a suscribir en el giro normal de sus negocios y operaciones sociales. Por lo anterior, el señor ANTONIO VARELA DIAZ, queda facultado para firmar las declaraciones comabiarias y demas documentos relacionados con las declaraciones, notificaciones, aportar y solicitar las pruebas que sean necesarias, desistir en general a realizar todo act necesario de tal forma que pueda cumplir con el mandato dado.-

C E R T I F I C A

Que segun documento privado del 22 de Febrero de 2005, inscrito en esta Camara de Comercio el 28 de Marzo de 2.005, bajo el No. 2.820 del libro respectivo, consta que WALTER TANAKA TATEKAWA C.C. 16.251-923 de Palmira, quien actua como representante legal de la sociedad PROCAPS S.A, otorga Poder Especial, Amplio y Suficiente al señor MARLON TATIS PAREDES C.C. No. 72.176.874, para que en representacion de PROCAPS S.A., suscriba declaraciones aduaneras, reportes y cualquier tipo de documentos relacionados con los tramites o registros de comercio exterior ante la direccion de impuestos y aduanas nacionales y/o cualquier entidad que haga sus veces, y para que responda todo tipo de requerimientos y/o solicitudes de informacion de las autoridades aduaneras en los ordenes distrital, departamental y nacional.-----

C E R T I F I C A

Que por Escritura Publica No.1.613 del 28 de Junio del 2.005, otorgada en la Notaria Segunda de Barranquilla, inscrita en esta Camara de Comercio el 18 de agosto del 2.005 bajo el No.2.913 del libro respectivo, consta que RUBEN MINSKI GONTOVNIK, C.C.No.7.463.928, en su condicion de Presidente y Representante Legal de la sociedad PROCAPS S.A., confiere poder especial amplio y suficiente a los siguientes señores que conforman el Grupo A y el Grupo B, para que conjuntamente suscriban contratos de suministro de mercancías y servicios con entidades oficiales, hasta por la suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS DE AMERICA (US\$800.000), liquidados a la tasa representativa del mercado vigente en el día que se realice la respectiva transaccion. GRUPO A: MIRIAM RODRIGUEZ DIAZ, C.C.No. 41.473.569. GRUPO B: NELSON SUAREZ CHAVEZ, C.C.No.79.417.971.-----.

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 nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su última Renovación fue el: 29 de Marzo de 2006.

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PROCAPS S.A.-----

NIT: 890.106.527-5.

La información sobre embargos de establecimiento se suministra en Certificados de Matrícula, la de contratos sujetos a registro, en Certificados Especiales.

mlajon

(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 Anne 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
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- (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).
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(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.

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

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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,

- 15 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
20 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.

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Drospirenone is known from DE 28 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.

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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).

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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-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.

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-17 α -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.

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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 antimineralocorticoid 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.

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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 oxyliminopregnane 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.

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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.

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- 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* 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.

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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 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 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 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 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.

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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 flashes, sweating attacks, palpitations, sleep disorders, mood changes, nervousness, anxiety,
30 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.

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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.

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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

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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.

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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.

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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.

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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 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 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 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 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 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, 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 diseases, disorders and symptoms associated with deficient endogenous levels of

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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.

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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.

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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

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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 8.

- 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

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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.

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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.

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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.

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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.

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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.

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

Example 4: Endometrial Protection

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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 flashes, 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.

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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.

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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_i 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_i 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.

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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.

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Example 6: Menopausal Symptoms

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

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Primary Objective: Hot flushes

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

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Synopsis

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

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- 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).

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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,

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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 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:

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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 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.

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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
post-menopausal women randomly assigned to one of 3 groups of 100 after giving their
15 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-17 α -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

sulfate, equilin sulfate, 17 β -dihydroequilin sulfate, 17 α -dihydroequilin sulfate, equilinen 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.

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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
25 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.

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.

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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.

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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.

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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.

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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 of a number
20 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;
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.

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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.

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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.

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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.

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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.

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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
20 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
25 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
30 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
35 6 mg; and

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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

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

National Application No.
PCT/IB 01/00041A. 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
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- *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

25 Apr 11 2001

Date of mailing of the international search report

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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

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INTERNATIONAL SEARCH REPORT

Information on patent family members

In International Application No

PCT/IB 01/00041

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WO 9507081 A	16-03-1995	NL 9301562 A	03-04-1995
		AU 1848899 A	29-04-1999
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		AU 7695294 A	27-03-1995
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WO 9827929 A	02-07-1998	DE 19654609 A	25-06-1998
		AU 5981098 A	17-07-1998

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2020
Bogotá, D C ,

Doctor
Gustavo Hollmann Restrepo
Apoderado

Oficio N° 8723

ASUNTO	Radicación PCT N°	04-117322
	Trámite	011
	Evento	379
	Actuación	440
	Folios	009

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor Reinaldo Pinilla Moreno, en su calidad de apoderado de Procaps S A , reúne los requisitos formales exigidos por la ley al momento de su presentación

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5 2, literal e), del capítulo quinto del título primero de la Circular Unica N° 10 de 2001


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

28 JUL 2006

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

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