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FORMULARIO ÚNICO DE OPOSICIÓN

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OPOSICIÓN A:

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| ☒ 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. | |

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Número del expediente: 05-130115

Solicitante: GADOR S.A.

**SOLICITUD
PUBLICADA**

Apoderado: JORGE E VERA VARGAS

Titulo de la nueva creación o denominación del signo: "COMPOSICIONES FARMACÉUTICAS SÓLIDAS QUE COMPRENDEN UNA COMBINACIÓN DE DROSPIRENONA, ETINILESTRADIOL Y UN AGENTE SURFACTANTE ADECUADO QUE PRESENTA UNA HOMOGENEIDAD DE CONTENIDO Y VELOCIDAD DE DISOLUCIÓN ASEGURADA PARA LA DROGA NO MICRONIZADA Y PROCEDIMIENTO PARA PREPARAR DICHA COMPOSICIÓN Y USO DE ESTA COMPOSICIÓN PARA PREPARAR UN MEDICAMENTO".

③ **OPOSICIÓN PRESENTADA POR:**

SOLICITANTE	Nombre: PROCAPS S.A	IDENTIFICACIÓN	
	Dirección: CALLE 80 No. 78b-201	C.C. ☐	NIT ☒
	Nacionalidad o Domicilio: COLOMBIA	C.E. ☐	Otro ☐
	Lugar de Constitución: BARRANQUILLA	Cual <u> </u>	
	Teléfono: (571)371 99 00 Fax: (571)373 08 18	Número <u>890.106.527-5</u>	
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REPRESENTANTE O APODERADO	Nombre: LAURA CATALINA SILVA BARRERA	IDENTIFICACIÓN	
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		Número <u>52.455.803</u> TP <u>147399</u>	

④ **FUNDAMENTOS DE LA OPOSICIÓN:**

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

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor:

Justificación:

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo 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: LAURA CATALINA SILVA BARRERA

FIRMA:

Laura Catalina Silva B.

C.C. 52.455.803

TP. 147399

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Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 05 130115

Asunto : Oposición a la solicitud de patente de Invención titulada
*"COMPOSICIONES FARMACÉUTICAS SÓLIDAS QUE
COMPRENDEN UNA COMBINACIÓN DE
DROSPIRENONA, ETINILESTRADIOL Y UN AGENTE
SURFACTANTE ADECUADO QUE PRESENTA UNA
HOMOGENEIDAD DE CONTENIDO Y VELOCIDAD DE
DISOLUCIÓN ASEGURADA PARA LA DROGA NO
MICRONIZADA, PROCEDIMIENTO PARA PREPARAR
DICHA COMPOSICIÓN Y USO DE ESTA COMPOSICIÓN
PARA PREPARAR UN MEDICAMENTO"*.

Solicitante : GADOR S.A.

Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 577 del 29 de junio de 2007

Yo, **LAURA CATALINA SILVA BARRERA**, abogada con tarjeta profesional N°
147399 del Consejo Superior de la Judicatura, en mi condición de apoderada de la
sociedad **PROCAPS S.A.** conformada bajo las leyes de la República de Colombia y

domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del título de la Patente de Invención denominada ***"COMPOSICIONES FARMACÉUTICAS SÓLIDAS QUE COMPRENDEN UNA COMBINACIÓN DE DROSPIRENONA, ETINILESTRADIOL Y UN AGENTE SURFACTANTE ADECUADO QUE PRESENTA UNA HOMOGENEIDAD DE CONTENIDO Y VELOCIDAD DE DISOLUCIÓN ASEGURADA PARA LA DROGA NO MICRONIZADA, PROCEDIMIENTO PARA PREPARAR DICHA COMPOSICIÓN Y USO DE ESTA COMPOSICIÓN PARA PREPARAR UN MEDICAMENTO"***, solicitada por GADOR S.A., y pido a Usted declarar fundada esta oposición y en consecuencia negar el título de la patente solicitada.

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular drospirenona y 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

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2.1. La solicitud objeto de la presente fue presentada el 27 de diciembre de 2005, reivindicando prioridad bajo la solicitud AR P01 01 04928 del 28 de diciembre de 2004 y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 577 del 29 de junio de 2007, página 614, N° publicación 93.

2.2. La solicitud colombiana 05 130115, objeto de la presente oposición, se refiere a Composiciones farmacéuticas sólidas que comprenden una combinación de Drospirenona, Etinilestradiol y un agente surfactante adecuado que presentan una homogeneidad de contenido y velocidad de disolución asegurada para la droga no micronizada, además reivindicán un procedimiento para preparar dicha composición y el uso de la misma en la preparación de un medicamento.

2.3. En primera instancia, se debe advertir que la reivindicación 43 se refieren al uso de una formulación para evitar la concepción y no a la composición farmacológica mediante el cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...) "*, los usos no están contemplados como patentables y sólo son materia objeto de patente los productos o procedimientos. Por lo tanto a luz de la norma, la presente reivindicación no sería susceptible de protección.

2.4. De conformidad con el artículo 14 de la Decisión 486 de la CAN en el que se consagra que: *"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"*, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de

prioridad de esta solicitud se encuentran los siguientes documentos que afectan el nivel inventivo de la presente solicitud:

- D1: US5975570 publicada el 02 de noviembre de 1999.
- D2: USRE37838E publicada el 10 de septiembre de 2002.
- D3: US2001/0020015 publicada el 06 de septiembre de 2001.
- D4: WO0115701 publicada el 08 de marzo de 2001.

2.5. Ahora bien, el documento D1, particularmente en las columnas 1 y 2, líneas 10 a 45 y en las reivindicaciones de la columna 4, revela un método para preparar composiciones farmacéuticas en unidades de dosificación mediante granulación húmeda de los ingredientes, empleando además solventes acuosos y tensioactivos. El método hace particular hincapié en la utilización de cantidades requeridas de tensioactivos para disolver o suspender el ingrediente activo. Dentro de los excipientes susceptibles de granulación por vía húmeda se encuentran: gelatina, gomas naturales como acacia, tragacanto, almidones, alginatos, azúcares, polivinilpirrolidona, derivados de celulosa como HPMC, poliviniloxazolidonas y diluentes farmacéuticos como lactosa, celulosa microcristalina, fosfato dicálcico, fosfato tricálcico, sulfato de calcio, dextrosa, manitol, sucrosa, agentes lubricantes que faciliten la operación de tableteo tal es el caso de: calcio y estearato de magnesio, ácido esteárico, talco y estearato alcalino. El principio activo susceptible de formular mediante dicho método consiste en una sustancia que requiera bajas dosificaciones, en especial del orden de miligramos por unidad de dosis, por ello los ejemplos de sustancias con actividad contraceptiva que se formulan en este sistema son etinil-estradiol, estrona, mestranol, las cuales corresponden a principios activos de carácter estrogénico. Pero también es posible formular en dicho sistema sustancias de carácter progestágeno como desogestrel, levo-desogestrel, norgestrel,

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gestodona y noretindrona. La publicación norteamericana también define un tercer componente susceptible de formularse en el sistema y corresponde a un tensioactivo que puede demostrar diversas características físicas y químicas de acuerdo con su estructura, pero dentro de ellos se encuentran los agentes de tensión superficial no iónicos como polisorbato 60 y polisorbato 80. Señala además que la cantidad de agente tensioactivo dependerá del ingrediente activo que se requiera suspender y granular, por ello se utilizan en cantidades menores del 0,01% en peso para que no se produzcan efectos tóxicos. En el ejemplo 1 de la publicación se establecen cantidades y proporciones de las sustancias que pueden formularse bajo esta metodología:

Materiales	Porcentaje	Mg/Tableta
Celulosa microcristalina	20.00	32.80
Lactosa 316	51.94	85.18
Fosfato cálcico dibásico	23.70	38.87
Dióxido de silicio coloidal	1.00	1.64
Croscarmelosa sódica	1.00	1.64
Estearato de magnesio	1.00	1.64
Povidona	0.14	0.23
Laurel-sulfato de sodio	0.0003	Trazas
Estradiol	1.22	2.00

En cuanto al procedimiento para fabricar las composiciones, el documento señala en la columna 3, líneas 41 a 50 que se puede seguir la siguiente secuencia de pasos: 1) suspender el estradiol, 2) mezclar el fosfato cálcico dibásico y la lactosa hasta obtener una mezcla homogénea, 3) secar la mezcla granulada, 4) someter a la operación de mezcla los demás excipientes, 4) comprimir la mezcla obtenida. De

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esta manera, las características técnicas del producto y del procedimiento, definidos en la solicitud de patente, se relacionan de manera directa con la materia contemplada en la publicación D1.

2.6.El documento D2 menciona combinaciones de agentes orales con actividad frente a la contracepción que consisten en 2.0 a 6.0 mg de 17 β -estradiol y 0.02mg de etinil estradiol y un gestágeno seleccionado entre 0.25 a 0.30 mg de drospirenona y 0.1 a 0.2 mg de acetato de ciproterona. De manera singular la publicación menciona la combinación específica de etinil-estradiol y drospirenona en la columna 6 líneas 28 a 35 cuando determina que la modalidad especial de dicha combinación debe corresponder a la asociación del estrógeno y gestágeno señalados. Como ventajas técnicas de las preparaciones que contienen las combinaciones de sustancias y que deben ser administradas durante 23 días y contener cantidades no menores a 30 μ g de etinil-estradiol se encuentran: la disminución significativa de la frecuencia en el desarrollo folicular, la generación de folículos con mayor diámetro y el control de los niveles hormonales de 17 β -estradiol. Dichas ventajas se encuentran reseñadas en la columna 5 líneas 5 a 27 del documento D2. De esta manera se observa cómo el documento D2 anticipa las características técnicas de la asociación reclamada por la solicitud y en consecuencia afecta los requisitos de patentabilidad.

2.7.El documento D3 publica en la página 2 incisos 9 a 17 y en la página 3 incisos 28 y 29 un régimen de administración oral que tiene como objetivo el manejo de la contracepción. El régimen comprende la administración secuencial de dos o más agentes progestágenos que presentan diferentes efectos en el endometrio y que pueden combinarse con un agente estrogénico por un periodo de 7 a 14 días. El componente estrogénico se emplea en dosis de 0.020 a 0.050 mg y el componente

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progestágeno se emplea en dosis de 0.065 a 2.0 mg. Los excipientes farmacéuticos que se emplean comúnmente en las formulaciones son: diluentes, saborizantes, solubilizantes, lubricantes, agentes suspensotes, aglutinantes, desintegrantes de tableta y materiales para encapsulación. Dentro de los diluentes se encuentran: almidón, lactosa, fosfato dicálcico, celulosa microcristalina, sucrosa, talco, carbonato de magnesio y caolín, entre otros. Dentro los excipientes líquidos se incluyen agua estéril, polietilenglicol, tensioactivos no iónicos y algunos aceites como sésamo y maní, que son ideales para formular los ingredientes activos en el sistema que se prefiera. En consecuencia, el documento D3 señalaba el camino para formular sustancias contraceptivas: estrógeno y gestágeno en formulaciones que presentan excipientes comunes como: tensioactivos no iónicos, diluentes, y lubricantes especialmente.

2.8.El documento D4 hace referencia a combinaciones farmacéuticas que contienen un primer agente activo que es 6β , 7β , 15β , 16β -dimetilen-3-oxo- 17α -preg-4-nano-21,17-carbolactona más conocido como drospirenona y como segundo ingrediente 17α -etinil-estradiol. Establece el documento en la página 11, ejemplo 1, líneas 15 a 30 que los núcleos para tableta contienen drospirenona micronizada en cantidad de 3.00mg, etinil-estradiol en cantidad de 0.03mg, lactosa monohidratada en cantidad de 48.17mg, almidón de maíz en cantidad de 14.40mg, almidón modificado en cantidad de 9.60mg, polivinilpirrolidona 25.000 en cantidad de 4.00mg y estearato de magnesio en cantidad de 0.80mg. La publicación señala en la página 9 líneas 10 a 23 que las composiciones pueden acompañarse de excipientes farmacéuticos necesarios para promover la disolución rápida de los agentes activos y además puede contener agentes diluentes entre los que se encuentran: lactosa, glucosa o sucrosa, manitol, sorbitol, xilitol, almidón de maíz o de papa, almidones modificados, lubricantes como talco, estearato de magnesio, estearato de calcio,

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silica coloidal o ácido esteárico, aglutinantes como polivinilpirrolidona, derivados de celulosa, carboximetil-celulosa, hidroxipropil-celulosa, entre otros excipientes farmacéuticos. De esta manera queda dibujado el camino para desarrollar sistemas de entrega farmacéuticos que contengan un gestágeno y un estrógeno como drospirenona y etinil-estradiol, presentes en formulaciones sólidas y acompañados de los excipientes farmacéuticos necesarios para mejorar la disponibilidad de los agentes activos, tal como la solicitud ha reclamado en las reivindicaciones 1 a 43.

2.9. Por lo tanto, este documento objeto de oposición a la luz de los documentos D1, D2, D3 y D4 carece evidentemente de nivel inventivo.

2.10. En consecuencia y de acuerdo con lo descrito anteriormente, se deriva que la solicitud colombiana 05 130115 de 27 de diciembre de 2005 no puede pretender un monopolio por patente toda vez que no cumple uno de los tres requisitos necesarios para su protección.

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

2.11.1. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *“Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”*. A la fecha de prioridad del 28 de diciembre de 2004, reivindicada por en virtud del documento AR P01 01 04928, es posible derivar, a partir de los documentos del estado de la técnica: D1, D2, D3 y D4 combinados en parejas, un sistema para formular agentes

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contraceptivos que contengan un principio activo estrogénico como etinilestradiol y un principio activo de orden gestágeno como drospirenona en combinación con una sustancia que disminuya la tensión superficial, con tamaño de partícula requerido sin que los activos se encuentren en tamaño micronizado, según lo definido en las reivindicaciones de la presente solicitud.

2.12. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial.”*. La solicitud pretendida no cumple con uno de los tres requisitos de patentabilidad.

2.13. Por todo lo anterior, atentamente solicito a usted, se sirva declarar fundada la presente oposición y negar el título de Patente de invención a la solicitud denominada ***“COMPOSICIONES FARMACÉUTICAS SÓLIDAS QUE COMPRENDEN UNA COMBINACIÓN DE DROSPIRENONA, ETINILESTRADIOL Y UN AGENTE SURFACTANTE ADECUADO QUE PRESENTA UNA HOMOGENEIDAD DE CONTENIDO Y VELOCIDAD DE DISOLUCIÓN ASEGURADA PARA LA DROGA NO MICRONIZADA, PROCEDIMIENTO PARA PREPARAR DICHA COMPOSICIÓN Y USO DE ESTA COMPOSICIÓN PARA PREPARAR UN MEDICAMENTO”***, solicitada por GADOR S.A., solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 577 de 29 de junio de 2007

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3. PRUEBAS

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

- D1: US5975570 publicada el 02 de noviembre de 1999.
- D2: USRE37838E publicada el 10 de septiembre de 2002.
- D3: US2001/0020015 publicada el 06 de septiembre de 2001.
- D4: WO0115701 publicada el 08 de marzo de 2001.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

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

5. ANEXOS

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

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

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4. Copias de los documentos:

- D1: US5975570 publicada el 02 de noviembre de 1999.
- D2: USRE37838E publicada el 10 de septiembre de 2002.
- D3: US2001/0020015 publicada el 06 de septiembre de 2001.
- D4: WO0115701 publicada el 08 de marzo de 2001.

6. NOTIFICACIONES

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

Señor Superintendente,

Laura Catalina Silva B.

LAURA CATALINA SILVA BARRERA

C.C. 52'455.803 de Bogotá

T.P.A. 147399 del C.S. de la J.



US005975570A

United States Patent [19]
Bosio**[11] Patent Number: 5,975,570**
[45] Date of Patent: Nov. 2, 1999**[54] COMPRESSED GAS STORAGE MEANS FOR
A VEHICLE OCCUPANT RESTRAINING
SYSTEM****[75] Inventor: Allen Charles Bosio, Leinzell,
Germany****[73] Assignee: TRW Occupant Restraint Systems
GmbH, Alfdorf, Germany****[21] Appl. No.: 08/963,968****[22] Filed: Nov. 4, 1997****[30] Foreign Application Priority Data**

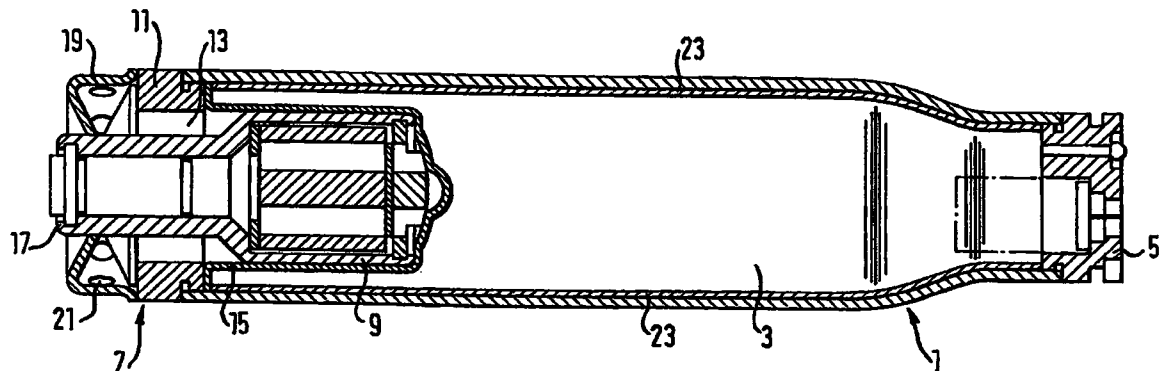
Nov. 8, 1996 [DE] Germany 296 19 437

[51] Int. Cl.⁶ B60R 21/26**[52] U.S. Cl. 280/741****[58] Field of Search 280/741****[56] References Cited****U.S. PATENT DOCUMENTS**

3,316,691 5/1967 Sesny et al. 55/66

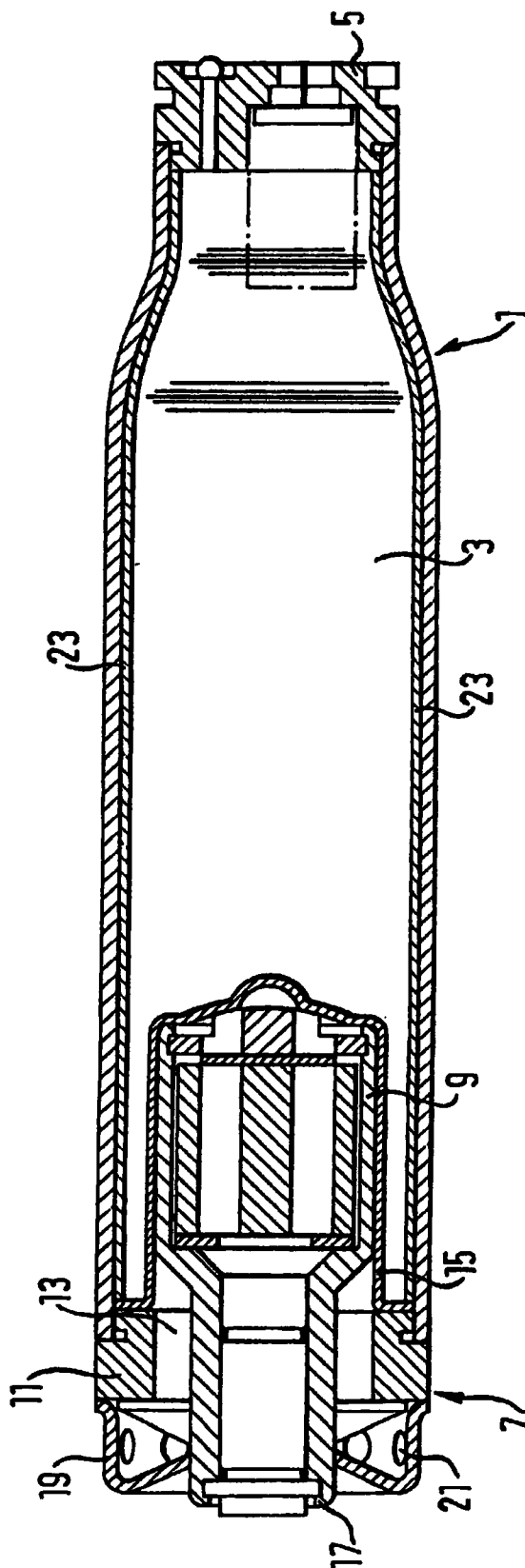
4,414,005 11/1983 DeBievre et al. 55/75
4,495,900 1/1985 Stockmeyer 123/1 A
4,836,255 6/1989 Schneiter et al. 280/741
5,031,932 7/1991 Frantom et al. 280/741
5,275,433 1/1994 Klobner et al. 280/741**FOREIGN PATENT DOCUMENTS**0049936 4/1982 European Pat. Off. .
2458741 1/1981 France .
1231784 5/1971 United Kingdom .**Primary Examiner—Kenneth R. Rice**
Attorney, Agent, or Firm—Tarolli, Sundheim, Covell,
Tummino & Szabo LLP**[57] ABSTRACT**

A compressed gas storage means for a vehicle occupant restraining system comprising a storage container having a chamber formed therein, the chamber containing gas stored under a high pressure and having an internal wall surface bearing a coating of a material with a high specific surface area.

4 Claims, 2 Drawing Sheets

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FIG. 1



COMPRESSED GAS STORAGE MEANS FOR A VEHICLE OCCUPANT RESTRAINING SYSTEM

FIELD OF THE INVENTION

The invention relates to a compressed gas storage means for a vehicle occupant restraining system comprising a storage container having a chamber containing gas stored under high pressure.

BACKGROUND ART

Compressed gas storage means, more especially for the inflation of a gas bag for a vehicle occupant restraining system, are opened in a crash by activation of small pyrotechnic charge so that the gas stored in the storage container may escape and cause deployment of the gas bag. In this respect the gas bag must completely deploy within an extremely short period of time, a high gas pressure being required for rapid filling of the gas bag and such gas pressure must be maintained in the final phase of deployment as well. A gas pressure which is only high at the outset on the contrary tends to be an obstacle for the initial part of deployment and is unable to ensure full deployment of the gas bag.

SUMMARY OF THE INVENTION

The invention is to provide a compressed gas storage means, in the case of which, without any change in volume, a larger amount of gas may be stored so that in the final phase of the deployment operation there is still sufficient gas for complete deployment of the gas bag. In the case of a compressed gas storage means of the type initially mentioned this is rendered possible by the invention because the inner wall surface of the chamber bears a coating of a material with a high specific surface area. Preferably, the material possesses a specific surface area within a range of 200 to 400 m²/g. In a particularly preferred embodiment of the invention the said material is an oxide or a molecular sieve and, most preferred, a zeolite.

Further features and advantages of the invention will be apparent from the following description of a preferred embodiment and from the following drawings, to which reference is had.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a compressed gas storage means in accordance with the invention as part of a gas bag module, in longitudinal section.

FIG. 2 represents a diagrammatic chart of variations in the internal pressure of the chamber as a function of time.

FIG. 3 is a diagrammatic chart of variations in mass flow from the chamber as a function of time.

DETAILED DESCRIPTION OF THE INVENTION

In FIG. 1 a compressed gas storage means is shown, which serves for the inflation of a gas bag, not illustrated, as part of a complete gas bag module. In the interior of the storage container 1 there is a chamber 3 charged with an inert gas such as for example argon or helium, or with air. However, it would be possible to employ other gases or gas mixtures utilized in industry. The gas stored in the chamber 3 is under a pressure of over 200 bar. A charging end 5 positioned at the front face is located opposite to a discharge

end 7. From the discharge end an ignition unit 9 extends into the interior of the chamber 3. The ignition unit 9 comprises a pyrotechnic charge which in a crash is fired in response to a signal. The end wall 11 at the discharge end 7 possesses a plurality of discharge openings 13 distributed evenly about a periphery, such openings being separated in the non-operated state of the unit by a wall 15 from the chamber 3. On a connection pin 17, extending out from the end wall 11, of the ignition unit 9 a diffusor baffle 19 is mounted which has numerous discharge openings 21. This baffle 19 of the storage container 1 extends into the interior of a gas bag, not illustrated, with the storage container and the gas bag forming a gas bag module.

The interior wall surface of the chamber 3 bears a coating 23 of a material with a high specific surface area, preferably a zeolite, the specific surface area of the material preferably being within a range of 200 to 400 m²/g. As a material with a high specific surface area other oxides or molecular sieves may also be employed. The specific surface area of the material may also be larger than 400 m²/g.

The manner of operation of the compressed gas storage means of the invention will be explained in the following:

Owing to the adhesion or adsorption forces acting on the gas molecules the coating 23 applied to the inner wall surface of the chamber 3 renders it possible for there to be a compaction of the gas introduced into the chamber on the surface of the coating until a liquid condition is attained. Accordingly, for the identical volume of the chamber 3 it is possible for a larger quantity of gas to be stored. In a crash the pyrotechnic charge located in the ignition unit 9 will be fired so that additional gas will flow into the interior of the chamber 3. The pressure in the chamber 3 is consequently so increased that the wall 15 will rupture and gas will flow through the discharge openings 13 through the diffusor baffle 19 and via the discharge openings 21 into the interior of the gas bag. With the reduction in the internal pressure the coating 23 will release the gas adsorbed on its surface so that in the final phase of the deployment operation such additional gas will be made available for complete deployment of the gas bag.

FIG. 2 diagrammatically shows the variation in pressure within the chamber 3 as a function of time (t). As described above, the internal pressure in the chamber will rise immediately following activation of the pyrotechnic charge in order, after rupture of the wall 15, to fall again sharply. In the case of a compressed gas storage means without a coating the drop in pressure is sharper or steeper than in the case of compressed gas storage means of the invention and the internal pressure in the chamber approaches the pressure of the surroundings more rapidly. In the final phase of deployment of the gas bag the internal pressure in the chamber of the compressed gas storage means of the invention is hence higher than in compressed gas storage means known so far.

Much the same applies for the variation with time of the mass flow from the chamber 3 as represented diagrammatically in FIG. 3. The release of the pyrotechnic charge firstly leads to a rise in the quantity of gas inside the chamber 3. After the rupture of the wall 15 the gas flows into the gas bag and causes the deployment thereof. However, owing to the adsorption of gas on the coating 23 the liberation of gas is delayed in time so that the final phase of the deployment operation a larger quantity of gas is made available than in the case of customary compressed gas storage means.

Moreover, with the use of the compressed gas storage means of the invention there is a smaller effect of the ambient temperature on the deployment operation, since the

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coating 23 functions as an accumulator and variations in temperature are more readily compensated for.

For the production of the compressed gas storage means of the invention the chamber 3 is treated with a slurry of the desired zeolite and dried at approximately 500 to 600° C. Preferably coating takes place by suspension of the material utilized for coating having a large specific surface area with the addition of a binding agent and following sintering at a high temperature and, if necessary, in an inert gas atmosphere. Filling of the compressed gas storage means with gas and/or with the pyrotechnic charge is performed using known technology.

Whereas the invention has been described with reference to a compressed gas storage means as a component of a gas bag module, the principle of the coating with a material having a high specific surface area can be employed in any other compressed gas storage means for vehicle occupant restraining systems.

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I claim:

1. A compressed gas storage means for a vehicle occupant restraining system comprising a storage container having a chamber formed therein, the chamber containing gas stored under a high pressure and having an internal wall surface bearing a coating of a material with a high specific surface area.

2. The compressed gas storage means as claimed in claim 1, wherein said material is an oxide or a molecular sieve.

3. The compressed gas storage means as claimed in claim 2, wherein said material is a zeolite.

4. The compressed gas storage means as claimed in claim 1, wherein said material has a specific surface area of 200 to 400 m²/g.

* * * * *

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120
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 (12) **Reissued Patent**
Spona et al.

(10) **Patent Number:** **US RE37,838 E**
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(54) **COMPOSITION FOR CONTRACEPTION**

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(73) Assignee: **Schering Aktiengesellschaft (DE)**

(*) Notice: This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/504,084**

(22) Filed: **Feb. 15, 2000**

Related U.S. Patent Documents

Reissue of:

(64) Patent No.: **5,824,667**
 Issued: **Oct. 20, 1998**
 Appl. No.: **08/742,147**
 Filed: **Oct. 31, 1996**

U.S. Applications:

(63) Continuation of application No. 08/268,996, filed on Jun. 30, 1994, now Pat. No. 5,583,129.

(30) **Foreign Application Priority Data**

Dec. 22, 1993 (DE) 4344462

(51) Int. Cl.⁷ **A61K 31/56; A61K 31/57**

(52) U.S. Cl. **514/170**

(58) Field of Search 514/170

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(57) **ABSTRACT**

A combination product for oral contraception is disclosed comprising an estrogen selected from 2.0 to 6.0 mg of 17β-estradiol and 0.020 mg of ethinylestradiol; and a gestagen selected from [0.25 to 0.30 mg of] drospirenone and [0.1 to 0.2 mg of] cyproterone acetate, followed by 5 or 4 pill-free or sugar pill days.

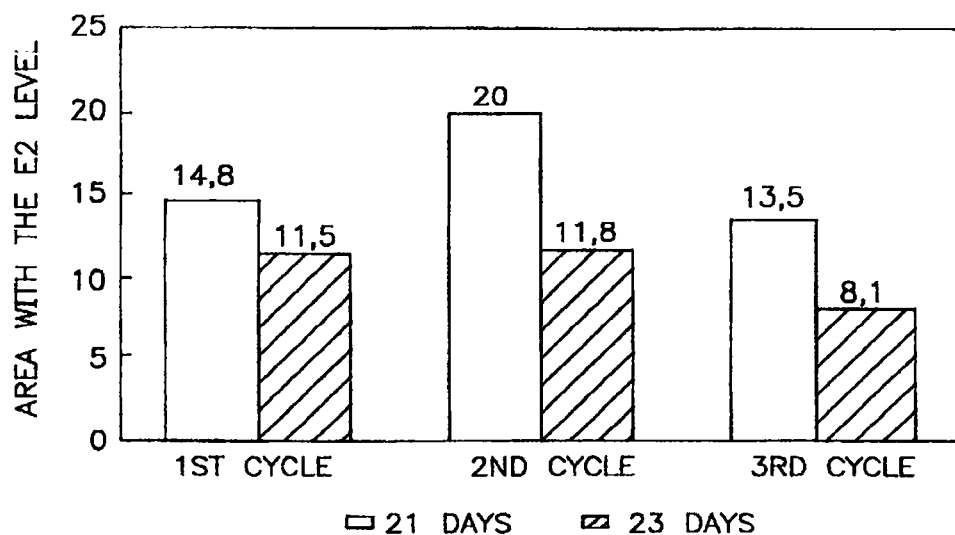


FIG. 1

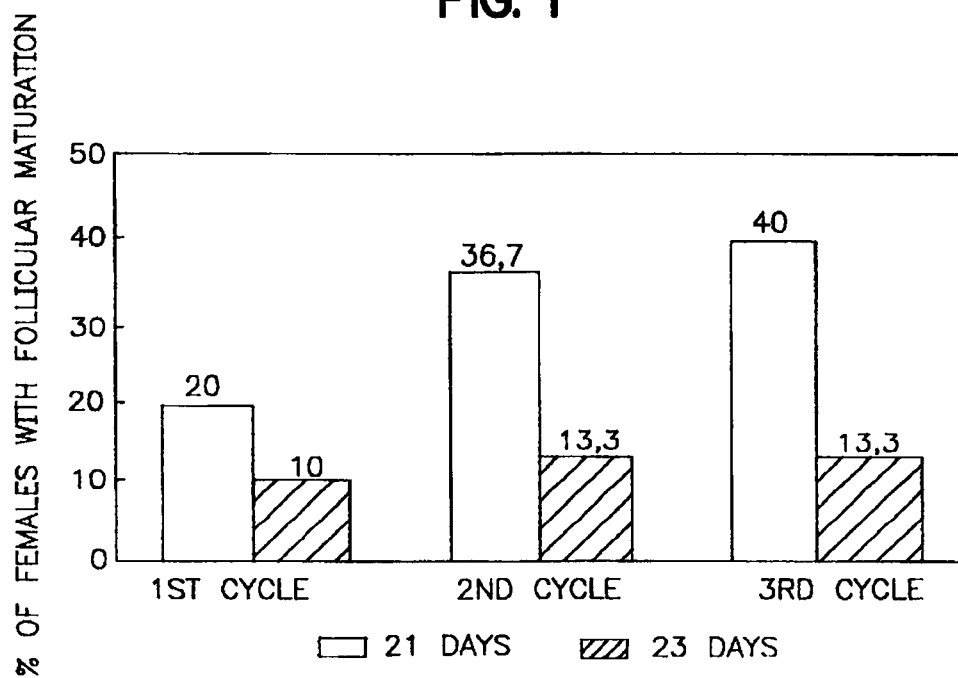


FIG. 2

COMPOSITION FOR CONTRACEPTION

Matter enclosed in heavy brackets [] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

[This] *This reissue application is a continuation of Ser. No. 09/503,952 now RE37564, filed on even date; application Ser. No. 742,147, filed Oct. 31, 1996, now U.S. Pat. No. 5,824,667, which is a continuation of the application Ser. No. 08/268,996 filed Jun. 30, 1994, now U.S. Pat. No. 5,583,129.*

DESCRIPTION

This invention relates to the common use of estrogens and gestagens for the production of a combination preparation for oral contraception and a corresponding pack containing this combination preparation.

Combination preparations for oral contraception are already known, for example, Femovan® [DE-PS 2 546 062] or Marvelon® [DE-OS 2 361 120]. These preparations consist of 21 active ingredient-containing (estrogen/gestagen) dosage units and 7 active ingredient-free coated tablets (sugar pills; placebos). The dose to be administered daily is uniformly high in each case (so-called single-phase preparations) and produces the desired contraceptive effect in the entire intake period and in the intake pause or during the intake of the placebos. In most preparations, a 7-day interruption of the intake of active ingredient-containing dosage units was considered necessary until quite recently to trigger a reliable withdrawal bleeding and thus to achieve a satisfactory cycle control.

Other preparations, which exhibit more than 21 dosage units containing an estrogenic and progestational active ingredient, and in which the intake pause is partially (Ijzerman, Pasquale) or completely (Kuhl) bridged over by estrogen-containing dosage units. In this case, it is possible that the synthetic estrogen ethinylestradiol otherwise contained in oral contraceptives is replaced partially or completely by a conjugated estrogen, preferably estradiol.

A combination preparation for substitution therapy and contraception for females before menopause (approximately starting from the 40th year of life) is known from EP-A-0 253 607. This combination preparation contains an estrogen from the group

17 β -Estradiol,
ethinylestradiol and
mestranol

as well as a gestagen from the group

levonorgestrel,
gestodene,
desogestrel,
3-ketodesogestrel and
norethindrone.

A thus selected composition is to offset hormonal irregularities in the transition phase of premenopause and to help alleviate the symptoms caused by the hormonal changeover of the female organism in this phase. Such a composition simultaneously assures a premenopausal female the contraceptive protection still necessary at this age.

The development of new oral contraceptives for females of reproductive age before premenopause was characterized during the last twenty years above all by the reduction of the estrogen and gestagen dosages.

The reduction of the daily hormone dose was connected with the expectation to minimize the frequency of undesired

side effects. Epidemiological data collected in the meantime confirm the desired trend toward better compatibility of lower-dosed preparations relative to cardiovascular complications [(1.) Thorogood, M., Oral Contraceptives and Cardiovascular Disease: An Epidemiologic Overview; Pharmacoeconomics and Drug Safety, Vol. 2: 3-16 (1993); (2.) Gerstman, B. B.; Piper, J. M.; Tomita, D. K.; Ferguson, W. J.; Stadel, B. V.; Lundin, F. E.; Oral Contraceptive Estrogen Dose and the Risk of Deep Venous Thromboembolic Disease, Am. J. E., Vol. 133, No. 1, 32-36 (1991); (3.) Lidegaard, O., Oral contraception and risk of a cerebral thromboembolic attack: results of a case-control study; BMJ Vol. 306, 956-63 (1993); (4.) Vessey, M.; Mant, D.; Smith, A.; Yeates, D.; Oral contraceptives and venous thromboembolism: findings in a large prospective study; BMJ, Vol. 292, (1986); (5.) Mishell, D. R., Oral Contraception: Past, Present and Future Perspectives; Int. J. Fertil., 36 Suppl., 7-18 (1991)].

It is assumed that a correlation exists above all between the level of the estrogen dose and the incidence of cardiovascular diseases. But the maintenance of the contraceptive effectiveness stands in the way of an extreme reduction of the daily estrogen dose. Although the ovulation-inhibiting effect of the low-dosed oral contraceptives is caused mainly by the gestagenic component, the estrogenic component also makes a significant contribution to the central inhibition action and to the ovarian suppression (ovulation inhibition). Moreover, the daily estrogen dose must not fall below the minimum dose ranges, so that a satisfactory cycle control can be assured (Der Frauenarzt [The Gynecologist]; 34, 7: 793 (1993)).

The lowest estrogen dose contained in an oral contraceptive on the market at this time is 20 μ g of ethinylestradiol, combined with 150 μ g of desogestrel (Mercilon). Although the cycle control of this preparation is, as expected, somewhat poorer in comparison to preparations with a higher estrogen dose, the high acceptance rate of Mercilon indicates a small clinical relevance of this drawback. But the observation, made identically in several studies, of a lesser ovarian suppression of the preparation containing 20 μ g of ethinylestradiol represents a clinically important problem. Obviously with this very low estrogen dose, in the case of many females, the maturation of follicles, which could be detected with ultrasonic studies or hormonal studies, results [(6.) Lunell, N. O.; Carlström, K.; Zador, G.; Ovulation inhibition with a combined oral contraceptive containing 20 μ g of ethinylestradiol and 250 μ g of levonorgestrel; Acta. Obstet. Gynecol. Scand. Suppl. 88: 17-21 (1979); (7.) Mall-Haefeli, M.; Werner-Zodrow, I.; Huber, P. R.; Klinische Erfahrungen mit Mercilon und Marvelon unter besonderer Berücksichtigung der Ovar-Funktion [Clinical Experience with Mercilon and Marvelon under special consideration of the ovary function]; Geburtsh. und Frauenheilk. [Obstetrics and Gynecology] 51, 35-38, Georg Thieme Verlag, Stuttgart-New York (1991); (8.) Strobel, E., Behandlung mit oralen Kontrazeptiva [Treatment with Oral Contraceptives]; Fortschr. Med. Vol. 110, No. 20 (1992); (9.) Letter to Editor, Contraception 45: 519-521 (1992); (10.) Teichmann, A. T.; Brill, K.; Can Dose Reduction of Ethinylestradiol in OCs Jeopardize Ovarian Suppression and Cycle Control? Abstract Book, VIIth World Congress on Human Reproduction, Bali, Indonesia (1993)].

The hormone determinations performed showed that functional granulosa cells that secrete 17 β -estradiol are involved. Each intake error in the case of females with clear ovarian activity, thus with follicular maturations, can result in a quick increase of gonadotropin production. The require-

ments for an ovulation would thus be present. It is estimated that approximately one third of females take oral contraceptives irregularly within one year of use (Gynpress, Volume 1, No. 3, 1990). The risk of a pregnancy is therefore high especially in the case of intake errors with the 20 μ g 5 ethinylestradiol preparations.

The object of this invention is an improved single-phase combination preparation for a female of reproductive age, who is not yet in premenopause, containing an estrogen and gestagen in each individual dosage unit, with the lowest possible estrogen content in each individual dosage unit, but also with a low total hormone content per administration cycle. 10

It has now been found that a pronounced ovarian suppression without frequent follicular maturations with low daily estrogen dosage, low total estrogen as well as low total hormone amount per administration cycle can be achieved by the use of a composition comprising an estrogen selected from

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

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

The terms "premenopause" and "menopause" are used within the scope of this invention in the meaning of the conventional definition, see, for example, "The Controversial Climacteric," P. A. of Keep et al., Ed., MTP press (1981), c.g., p. 9.

The daily hormone dose is kept to a very low level here, while the usual 21-day intake is extended by two or three days. The remaining 5 or 4 days of a cycle are preferably bridged over by placebos, to avoid intake errors, or by 5 or 4 intake-free days.

According to a preferred embodiment of this invention, this relates to the use of a composition comprising an estrogen selected from

>2.0 to 6.0 mg of 17 β -estradiol and
0.020 mg of ethinylestradiol;
and a gestagen selected from
>0.06 to 0.075 mg of gestodene,
>0.100 to 0.125 mg of levonorgestrel,
>0.10 to 0.15 mg of desogestrel,
>0.10 to 0.15 mg of 3-ketodesogestrel,
0.25 to 0.30 mg of drospirenone,
[0.1 to 0.2 mg of] cyproterone acetate,
0.2 to 0.3 mg of norgestimate and
0.50 to 0.75 mg of norethisterone

for the production of a form of dosage for contraception as described above.

In addition, this invention relates to a combination product for oral contraception, which comprises

a) 23 or 24 dosage units, each containing an estrogen selected from
>2.0 to 6.0 mg of 17 β -estradiol and
0.020 mg of ethinylestradiol;
and a gestagen selected from
>0.06 to 0.075 mg of gestodene,
>0.100 to 0.125 mg of levonorgestrel,
>0.10 to 0.15 mg of desogestrel,
>0.10 to 0.15 mg of 3-ketodesogestrel,
[0.25 to 0.30 mg of] drospirenone,
[0.1 to 0.2 mg of] cyproterone acetate,
0.2 to 0.3 mg of norgestimate and
0.50 to 0.75 mg of norethisterone

and

b) 5 or 4 sugar pills or other indications to show that the daily administration of 23 or 24 dosage units is to be followed by 5 or 4 pill-free or sugar pill days are to be followed.

Further embodiments according to the invention follow from the features of the subclaims.

An especially preferred combination preparation according to this invention comprises 23 dosage units, each containing 20 μ g of ethinylestradiol and 75 μ g of gestodene and 5 sugar pills or other indications to show that no dosage unit or a sugar pill is administered during the last 5 days of the menstrual cycle. 25

The clinical study briefly described below was performed with ethinylestradiol as estrogen and gestodene as representative of the substance class of the gestagens possible according to the invention. All possible combinations of ethinylestradiol or estradiol according to the invention in the indicated dosages with one of the selected gestagens in the indicated dosages as 23- or 24-day preparations exhibit the advantages according to the invention. 30

The 23-day administration of 20 μ g of ethinylestradiol in combination with 75 μ g of gestodene results, in comparison to the 21-day administration a stronger ovarian suppression. In a double-placebo, randomized study on healthy females with normal ovarian function, groups of 30 test subjects each received the combination preparation either once daily over 21 or 23 days as well as placebos on 7 or 5 days (to assure the double-placebo nature of the study). 35

The treatment began after an ovulatory, untreated preliminary cycle on the first day of the menstrual bleeding of the subsequent cycle and extended altogether over three treatment cycles. The study was concluded with an untreated follow-up cycle.

The ovarian suppression was measured based on the level of the endogenous 17 β -estradiol level and the size of follicular structures. The results show that the 17 β -estradiol levels with 23-day intake of the test preparation were significantly lower ($p < 0.05$) in comparison to the 21-day administration (FIG. 1). 40 50 55

In accordance with this finding, the number of females with follicular maturations was also clearly higher in the 21-time administration relative to the 23-time administration (FIG. 2).

The intake interval extended only by two days surprisingly produces a significantly greater ovarian suppression with unchangingly low daily doses. The combination preparation according to the invention thus achieves the effectiveness previously known for preparations with a daily content of 30 μ g of ethinylestradiol, although the daily ethinylestradiol dose is 33% lower and also the total dose per cycle is 27% lower. 60 65

The advantages of a combination preparation for oral contraception to be administered over 23 days relative to the usual 21-day preparations with less than 30 μg of ethinylestradiol can be characterized as follows:

1. A significantly lower frequency of follicular developments in the user (maximum of 13% in females who received the 23-day preparation relative to a maximum of 40% among those who received the 21-day preparation). This means a greater contraceptive reliability of the 23-day preparation, especially in the case of previous intake errors. The danger of "breakthrough ovulations" is smaller.
2. The occurrence of large follicles of more than a 30 mm diameter is extremely rare. The development of ovarian cysts is improbable with the 23-day preparation in comparison to the 21-day preparation.
3. The recruitment of dominant follicles is suppressed in the shortened intake-free pause.
4. The endogenous 17 β -estradiol levels are suppressed easily controllably in the case of the majority of the users of the 23-day preparation. Clinical symptoms such as breast tenseness, premenstrual syndrome and menstrual disorders; which can be attributed to increased and greatly fluctuating estrogen levels, are observed with the 23-day preparation with clearly lower frequency.

In summary, an intake, extended by two (or three) days, of preparations containing 20 μg of ethinylestradiol in each daily dosage unit can produce the above-mentioned advantages, without the daily dose having to be raised to the previously largely used level of 30 μg of ethinylestradiol.

The formulation of an estrogen and gestagen for the use according to the invention or for a combination preparation according to the invention takes place completely analogously as it is already known for usual oral contraceptives with 21-day intake period of the active ingredients, such as, for example, Femovang (ethinylestradiol/gestodene) or Microgynon® (ethinylestradiol/levonorgestrel).

A pack containing a combination preparation according to the invention is also designed analogously to packs for already known oral contraceptives on the market with the variation that instead of the usual 21 dosage units containing the active components, now 23 or 24 such dosage units and 5 or 4 sugar pills are present or else contain other suitable indications that 5 or 4 days are to be bridged over until continuation of the intake of active ingredient-containing dosage units.

Moreover, reference is made to the statements made in EP-A 0 253 607, especially also to the statements there for determination of equivalent amounts of ethinylestradiol and 17 β -estradiol, on the one hand, and various gestagens, such as levonorgestrel, desogestrel, 3-ketodesogestrel and gestodene, on the other hand.

For further details for the determination of dose equivalents of various gestagenic active ingredients, reference is made to "Probleme der Dosisfindung: Sexualhormone" [Problems of Dose-Finding: Sex Hormones]; F. Neumann et al. in "Arzneimittelforschung" (Pharmaceutical Agent Research) 27, 2a, 296-318 (1977), as well as to "Aktuelle Entwicklungen in der hormonalen Kontrazeption" [Current Developments in Hormonal Contraception]; J.H. Kuhl in "Gynäkologie" [Gynecologist] 25: 231-240 (1992).

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1: Area with the 17 β -estradiol level in groups of 30 females, who are treated with an oral contraceptive (75 μg

of gestodene+20 μg of ethinylestradiol) in 21- or 23-day administration interval over three cycles.

FIG. 2: Number of females in %, who showed follicular developments (>13 mm diameter) with 21- or 23-day treatment with an oral contraceptive (75 μg of gestodene+20 μg of ethinylestradiol).

We claim:

1. A combination product for oral contraception, comprising

- (a) 23 or 24 dosage units, each containing an estrogen selected from
>2.0 to 6.0 mg of 17 β -estradiol and
0.020 mg of ethinylestradiol;
and a gestagen selected from
[0.25 to 0.30 mg of] drospirenone and
[0.1 to 0.2 mg of] cyproterone acetate, in an amount which is equivalent to 75 μg of gestodene.

and

- b) 5 or 4, respectively, active ingredient-free placebo pills or other indications to show that the daily administration of the 23 or 24 dosage units respectively, is to be followed by 5 or 4, respectively pill-free or placebo pill days.

2. A combination preparation for oral contraception according to claim 1, wherein the estrogen is ethinylestradiol.

3. A combination preparation of claim 2, wherein the gestagen is cyproterone acetate.

4. A combination preparation of claim 2, wherein the gestagen is drospirenone.

5. A combination preparation according to claim 1, wherein the estrogen is present in a dose of 20 μg of ethinylestradiol or an equivalent dose of 17 β -estradiol and the gestagen is present in a dose equivalent to 75 μg of [gestadene] gestodene.

6. A combination preparation according to claim 1, which comprises 23 dosage units and 5 placebo pills or other indications to show that no dosage unit or a placebo pill is administered during the last 5 days of the menstrual cycle.

7. A combination preparation according to claim 1, which comprises 23 dosage units, each containing 20 μg of ethinylestradiol and a dose of cyproterone acetate or drospirenone equivalent to 75 μg of gestodene and 5 placebo pills or other indications to show that no dosage unit or a placebo pill is administered during the last 5 days of the menstrual cycle.

8. A combination preparation of claim 1, wherein the estrogen is 17 β -estradiol.

9. A combination preparation of claim 8, wherein the gestagen is cyproterone acetate.

10. A combination preparation of claim 8, wherein the gestagen is drospirenone.

11. A combination preparation of claim 4, which comprises 23 dosage units and 5 placebo pills or other indications to show that no dosage unit or placebo pill is administered during the last 5 days of the menstrual cycle.

12. A combination preparation of claim 4, which comprises 24 dosage units and 4 placebo pills or other indications to show that no dosage unit or placebo pill is administered during the last 4 days of the menstrual cycle.

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13. A combination product for oral contraception, comprising

(a) 23 or 24 daily dosage units, each containing 0.020 mg of ethinylestradiol, and an amount of drospirenone which is equivalent to 75 μ g of gestodene, and

(b) 5 or 4, respectively, active ingredient-free placebo pills or other indications to show that the daily administration of the 23 or 24 dosage units, respectively, is to be followed by 5 or 4, respectively, pill-free or placebo pill days,

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wherein each of the dosage units containing drospirenone contains the same amount of drospirenone.

14. A combination preparation of claim 13, which comprises 23 dosage units and 5 placebo pills or other indications to show that no dosage unit or placebo pill is administered during the last 5 days of the menstrual cycle.

15. A combination preparation of claim 13, which comprises 24 dosage units and 4 placebo pills or other indications to show that no dosage unit or placebo pill is administered during the last 4 days of the menstrual cycle.

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US 20010020015A1

(19) **United States**(12) **Patent Application Publication** (10) **Pub. No.: US 2001/0020015 A1**
Kafrissen et al. (43) **Pub. Date: Sep. 6, 2001**(54) **COMBINATION PROGESTIN ORAL
CONTRACEPTIVE REGIMEN**provisional of provisional application No. 60/057,
109, filed on Aug. 27, 1997.(76) **Inventors: Michael Kafrissen, Gladstone, NJ
(US); Haya Taitel, Gladstone, NJ (US)****Publication Classification**

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AUDLEY A. CIAMPORCERO JR.**JOHNSON & JOHNSON****ONE JOHNSON & JOHNSON PLAZA****NEW BRUNSWICK, NJ 08933-7003 (US)**(51) **Int. Cl.⁷ A61K 31/57**(52) **U.S. Cl. 514/171**(57) **ABSTRACT**(21) **Appl. No.: 09/833,439**(22) **Filed: Apr. 12, 2001****Related U.S. Application Data**(60) **Division of application No. 09/137,401, filed on Aug.
20, 1998, now Pat. No. 6,251,956, which is a non-**

An oral contraception regimen which comprises sequentially administering two or more progestational agents exhibiting different effects on the human endometrium in combination with an estrogen. The invention is also directed to an extended use oral contraception regimen comprising the sequential administration of two or more progestational agents in combination with an estrogen.

COMBINATION PROGESTIN ORAL CONTRACEPTIVE REGIMEN

FIELD OF THE INVENTION

[0001] The present invention is directed to a combination hormonal regimen for human oral contraception. More particularly, the present invention is directed to an oral contraception regimen which comprises sequentially administering two or more progestational agents exhibiting different effects on the human endometrium in combination with an estrogen. The invention is also directed to an extended use oral contraception regimen comprising the sequential administration of two or more progestational agents in combination with an estrogen.

BACKGROUND OF THE INVENTION

[0002] Oral contraception formulations, containing a combination of a progestin and an estrogen, have been known for some time. A number of different regimens for controlling ovulation and conception with these hormones have been developed. Conventional regimens may provide consistent dosage of either an estrogen or progestin or both throughout the period of administration, or they may vary the amount of estrogen or progestin by increasing or decreasing the dosage employed during the period of administration. For instance, U.S. Pat. Nos. 4,616,006 and 4,390,531 disclose triphasic oral contraception regimens wherein the dosage of progestin is varied in three sequences during the 21 day administration period in an effort to minimize side effects and optimize contraceptive activity.

[0003] A disadvantage inherent in the current oral contraception regimens is the incidence of abnormal intermenstrual or "breakthrough" bleeding. In general, the intended bleeding pattern with oral contraceptives is usually predictable and occurs during the seven day drug free interval following 21 days of active drug administration. Breakthrough bleeding refers to incidences of bleeding or spotting during the 21 day administration period. Breakthrough bleeding or spotting is reported to occur in about 20-30% of women. The incidence of breakthrough bleeding is the highest during the first few months of treatment and appears to be related to the dose and nature of the hormonal components as well as idiosyncratic responses. Another related problem with conventional oral contraceptive regimens is the occurrence of early withdrawal flow which is any bleeding or spotting during the drug administration interval which continues without interruption into the period wherein drug administration is withdrawn. Since discontinuation of a method of contraception because of abnormal intermenstrual bleeding continues to be an important factor leading to drug discontinuation and unintended pregnancy, there is a need for combined oral contraceptive formulations that meet the various clinical demands of the user and which provide the most acceptable pattern of bleeding.

[0004] Extended use regimens have been investigated wherein oral contraceptives are administered for up to three months between cycles. A three month trial of a regimen of oral contraceptives that reduces the frequency of menstruation was first described by Loudon, NB, Br.Med.J. 1977;2:487-90. The advantages of such regimens are that they offer freedom from menstrual flow and premenstrual symptoms for extended periods of time and are generally

easier to follow. Such extended use regimens may also have therapeutic use in dysmenorrhea, menorrhagia, premenstrual-type symptoms and menstrual migraine. Sulalc et al., Obstet-Gynecol 1997;89: 179-83 in a retrospective analysis, reports that 74% of the patients treated with 6 weeks of continuous active pills were stabilized and that the extended oral contraceptives regimen delayed the onset and severity of reported complaints. However, such extended use regimens are hampered by a high incidence of breakthrough bleeding, which is a common cause for discontinuation of the regimen.

[0005] Accordingly, there is a need for an oral contraceptive treatment regimen which reduces the incidence of bleeding abnormalities. As will be seen, there is also a related need for an oral contraceptive treatment regimen which achieves this reduction in the incidence of bleeding abnormalities while exhibiting a favorable effect on endometrial morphology.

[0006] There is also a need for an extended use oral contraceptive treatment regimen which achieves effective contraception but which exhibits a reduced incidence of bleeding abnormalities.

[0007] Different progestins in combined oral contraceptives appear to be associated with different bleeding patterns. While the mechanism for bleeding irregularities is still poorly understood, applicants have observed different patterns of breakthrough bleeding and spotting in comparative studies of the combination oral contraceptives norgestimate/ethinyl estradiol versus levonorgestrel/ethinyl estradiol. The variation in the bleeding patterns was more pronounced in those patients who were not taking oral contraceptives in the cycles prior to the study. In general, the overall proportions of breakthrough bleeding episodes were similar, but the patterns differed.

[0008] Progestational agents also differ in their effects on the endometrium. This can range from a proliferative or secretory endometrium to a non-vascular or atrophic condition which can resemble the postmenopausal histological structure. These effects are manifested by morphological changes in the endometrial glands, spiral capillaries, endometrial stroma and epithelial tissues. Cycle control during oral contraceptive use is related to the pattern of endometrial maturation. Thus, depending on the progestational agent used, one can detect histological differences between preparations which could subsequently influence the bleeding patterns. The endometrial morphology appearance has been observed to be different between norgestimate and levonorgestrel formulations. After six months treatment with norgestimate/ethinyl estradiol, well preserved lining epithelium was observed corresponding to midcycle or early secretory phase of the normal menstrual cycle. (Rabe, T. et al, Gerbutsch Fauenheilk 1986;46:883). Norgestimate was found to have an endometrial sparing effect in primates in comparison to other progestins. (Wilborn, WH et al, 1984, 4th Annual Meeting of Ala. Academy of Science, Tuscaloosa, Ala.). In general, the findings during treatment in humans with norgestimate containing oral contraceptives indicate a secretory transformation of well developed endometrium which was found however incapable of supporting an implanted blastocyte. In contrast, women treated with levonorgestrel containing oral contraceptives generally exhibit atrophic endometrial appearance with diminished gland diameter and glandular epithelial.

SUMMARY OF THE INVENTION

[0009] The present invention relates to a combination progestin and estrogen hormonal method and regimen for human contraception involving the sequential administration of two or more different progestational agents in combination with an estrogen comprising the steps of:

[0010] (a) administering a contraceptively effective amount of an endometrial sparing progestin in combination with an estrogen in single daily doses for a period of 7-14 days followed by;

[0011] (b) administering a contraceptively effective amount of an atrophizing progestin in combination with an estrogen in single daily doses for a period of 7-14 days;

[0012] (c) repeating steps (a) and (b) for a period of 21-90 days;

[0013] (d) withdrawing the administration for a period of 6-8 days; and

[0014] (e) repeating steps (a)-(d) continuously.

[0015] In a further embodiment, the invention provides a method of reducing breakthrough bleeding resulting from the administration of an effective ovulation suppressing amount of a combination progestin/estrogen oral contraceptive comprising administering an atrophizing progestin for 7-14 days, followed by administering an endometrial sparing progestin for 7-14 days and repeating this cycle for a period of 21-90 days before withdrawing the oral contraceptive for 6-8 days.

[0016] In a further embodiment, the invention relates to a method of reducing bleeding abnormalities in an extended use trimonthly oral contraceptive treatment regimen in accordance with the above regimen wherein the oral contraceptive is administered for a period of about 90 days prior to withdrawal.

[0017] Another aspect of the invention relates to a pharmaceutical package in the form of a tablet dispenser containing single daily doses of the combination oral contraceptive designed to administer the above mentioned method.

DETAILED DESCRIPTION

[0018] In accordance with the present invention, a combination progestin oral contraceptive regimen is provided which involves alternating an endometrial sparing progestin with an atrophizing progestin at intervals which may alter endometrial morphology thereby reducing breakthrough bleeding by preventing both irregular shedding of atrophied endometrium and the breakdown of very glandular endometrium in the later phases of continuing stimulation. By providing a balance of these two effects in sequential phases, the method may permit prolonged intervals between withdrawal bleeds.

[0019] The term "Endometrial Sparing" progestin means any compound which exhibits progestational activity and which induces a secretory endometrial morphology with a well preserved glandular structure. Examples of endometrial sparing progestins are norgestimate and norethindrone.

[0020] As used herein, the term "atrophizing progestin" refers to any compound which exhibits progestational activ-

ity and which induces an atrophic endometrial morphology with diminished gland diameter and glandular epithelial. Examples of atrophizing progestins are desogestrel, gestodene and levonorgestrel.

[0021] As stated, applicants have observed different bleeding patterns associated with different progestins. In a randomized comparative study of norgestimate/ethinyl estradiol (NGM/EE 250/35) versus levonorgestrel/ethinyl estradiol (LNG/EE 150/30), different patterns of breakthrough bleeding and spotting were observed. In general, the overall proportions of bleeding episodes were similar, however, the patterns (i.e. when in the cycle the episode occurred) were different. Thus, by making use of this observation concerning the difference in bleeding patterns and the knowledge of the different endometrial morphology associated with the different progestins, a method of reducing the incidence of breakthrough bleeding is obtained by combining the use of progestins exhibiting these different characteristics in the manner of this invention.

[0022] In accordance with the present invention, the combination progestin oral contraceptive composition is administered for a period of 21-90 days. This is followed by a period of 6-8 days in which the hormones are withdrawn to allow normal menstruation. Day one of the cycle is defined as the first day of administration. The days are then numbered sequentially until the hormone is withdrawn and menstruation occurs. A placebo or other hormone-free agent such as an iron supplement may be administered during the withdrawal phase.

[0023] The combination progestin contraceptive composition of the present invention comprises 21-90 separate dosage units intended for single daily dosage administration. The composition consists essentially of; a first phase of 7-14 dosage units containing an atrophizing progestin in combination with an estrogen in admixture with a pharmaceutically acceptable carriers; a second phase of 7-14 dosage units containing and endometrial sparing progestin in combination with an estrogen and a pharmaceutically acceptable carrier and, optionally, additional phases of alternating atrophizing progestin and endometrial sparing progestin in combination with an estrogen for a total period of 21-90 days. The composition may optionally contain 6-8 daily dosage units of hormone free units. The dosage and nature of the estrogen component will generally remain constant throughout the cycle while the nature of the progestin is sequentially alternated. The dosage of the progestin in each phase may also be varied as necessary to achieve maximum effect.

[0024] Any conventional estrogen may be employed as the estrogenic component of the combination oral contraceptive of the present invention. Preferably, the estrogen component is employed in a daily dosage equivalent to about 0.020-0.050 mg of ethinyl estradiol, preferably about 0.030 mg ethinyl estradiol equivalent.

[0025] The progestin component is preferably administered in a daily dosage corresponding in progestational activity to 0.065-2.0 mg norethindrone per day. The dosage of the progestin component may also be varied in biphasic or triphasic sequences so that less progestin is administered in the early stage of administration with increasing dosages utilized in the latter stages of administration. For example, a biphasic dosage may be utilized wherein the dosage of endometrial sparing progestin administered in the first phase

of administration may correspond in progestational activity to 0.065-0.75 mg norethindrone per day, while the dosage of atrophizing progestin administered in the second stage may range in progestogenic activity from 0.25-2.0 mg norethindrone per day. Similarly, the dosage of progestin may be adjusted in a triphasic manner as disclosed in U.S. Pat. Nos. 4,616,006 and 4,390,531. It may also be desirable to administer the estrogen component alone for the first 1-7 days of administration following the onset of menses as disclosed in U.S. Pat. Nos. 4,921,843 and 5,280,023.

[0026] The combination progestin regimen of the present invention is particularly useful for trimonthly extended use continuous therapy wherein the hormones are administered continuously for a period of up to three months before administration is withdrawn and withdrawal bleeding occurs. It is contemplated that such a regimen would involve alternating the administration of the endometrial sparing progestin with the atrophizing progestin during the three month period of administration. For example, the endometrial sparing progestin/estrogen combination would be administered for a period of about 7-14 days followed by administration of the atrophizing progestin/estrogen combination for a period of about 7-14 days. The two progestin/estrogen combinations would then be alternated in sequence for the three month extended use period of administration followed by a one week withdrawal flow interval. By alternating the use of the two progestins having differing effects on the endometrium, it is contemplated that the incidence of intermenstrual bleeding would be reduced allowing for the use of the extended regimen with a minimum of adverse effects.

[0027] The described dosages are generally preferred, but, of course, may be adjusted to provide the optimal therapeutic response depending upon the requirements of the patient, the weight and age of the patient, the particular hormone combination composition employed and the relative potency of the drugs involved. The determination of optimum dosages for a particular situation is within the skill of the medical arts.

[0028] In accordance with the present invention, the estrogen and progestin agents are preferably administered together orally in association with a pharmaceutically acceptable carrier. In general, the active agents may be combined with one or more pharmaceutically acceptable carriers, for example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules or suspensions containing, for example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 10 to about 50% of sugar, and elixirs containing, for example from about 20 to 50% ethanol, and the like, together with the usual additives or vehicles, in accordance with generally acceptable pharmaceutical practice. Such pharmaceutical preparations may contain, for example, from about 0.05 up to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight. While the estrogen and progestin components are preferably combined for oral administration, the estrogen and progestin components may be administered separately or parenterally.

[0029] The carrier may be one or more substances which act as diluents, flavoring agents, solubilizers, lubricants,

suspending agents, binders or tablet disintegrating agents as well as encapsulating materials. Suitable solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose, talc, magnesium carbonate, kaolin and the like. Suitable liquid carriers include sterile water, polyethylene glycol, non-ionic surfactants and edible oils such as peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents and antioxidant agents, for example, vitamin E, ascorbic acid, BHT and BHA.

[0030] The active agents may also administered by other art recognized means as practiced in the pharmaceutical arts. For example, the estrogen and progestin alone or in combination may be formulated for administration transdermally via a skin patch, by intramuscular injection, contained within an inert matrix which is implanted within the body and in a depot state, or intravaginally in a matrix that slowly releases the active compositions.

[0031] The active compounds may also be administered parenterally. Solutions or suspensions of the active components can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[0032] The pharmaceutical compositions are preferably packaged in the form of a pharmaceutical kit or package in which the daily dosages are arranged for proper sequential administration. This invention also relates, therefore, to a pharmaceutical package which contains the combination estrogen and progestin active agents in individual dosage units in a synchronized, fixed sequence, wherein the sequence corresponds to the oral contraceptive regimen of the present invention.

[0033] For example, the pharmaceutical package can be in the form of a kit containing individual tablets arranged sequentially and consisting of 7-14 single daily doses of the endometrial sparing progestin in combination with the estrogen, followed by 7-14 single daily doses of the atrophizing progestin in combination with the estrogen. This sequence of tablets may be alternated for a total of 21-90 tablets. Finally, the active agent containing tablets may be optionally followed with up to seven placebo tablets so that a tablet may be administered each day continuously.

[0034] The method of the present invention can be further understood by the following examples, but should not constitute a limitation thereof.

EXAMPLE 1

[0035] Uniphasic Dosage Regimen

[0036] On days 1-10 inclusive, 0.035 mg of ethinyl estradiol with 0.250 mg of norgestimate is administered daily. From Day 11-21, inclusive, 0.035 mg of ethinyl estradiol with 0.150 mg levonorgestrel is administered daily. From days 22-28, inclusive, a placebo is administered during which time menstruation occurs. This regimen is illustrated in Table I.

TABLE I

Day	Estrogen	Progestin
1-10	0.035 mg EE	0.250 mg NGM
11-21	0.035 mg EE	0.150 LNG
22-28	Placebo	

EE = Ethinyl Estradiol
 NGM = Norgestimate
 LNG = Levonorgestrel

EXAMPLE 2

[0037] Biphasic Dosage Regimen

[0038] A Biphasic Dosage regimen is utilized in accordance with the regimen set forth in the following Table II.

TABLE II

Day	Estrogen	Progestin
1-10	0.035 mg EE	0.180 mg NGM
10-21	0.035 mg EE	0.150 mg LNG
21-28	Placebo	

EXAMPLE 3

[0039] Triphasic Dosage Regimen

[0040] A Triphasic dosage regimen is utilized in accordance with the regimen set forth in the following Table III.

TABLE III

Day	Estrogen	Progestin
1-7	0.035 mg EE	0.180 mg NGM
8-14	0.035 mg EE	0.215 mg NGM
15-21	0.035 mg EE	0.150 mg LNG
21-28	Placebo	

EXAMPLE 4

[0041] Trimonthly Extended Use Regimen

[0042] A trimonthly extended use regimen is utilized in accordance with the regimen set forth in the following Table IV.

TABLE IV

Day	Estrogen	Progestin
1-14	0.035 mg EE	0.250 mg NGM
15-28	0.035 mg EE	0.150 LNG
29-43	0.035 mg EE	0.250 mg NGM
44-57	0.035 mg EE	0.150 mg LNG
58-71	0.035 mg EE	0.250 mg NGM
72-83	0.035 mg EE	0.150 mg LNG
84-90	placebo	

1. A combination progestin and estrogen hormonal method and regimen for human contraception involving the sequential administration of two or more different progestational agents in combination with an estrogen comprising the steps of:

- (a) administering a contraceptively effective amount of an endometrial sparing progestin in combination with an estrogen in single daily doses for a period of 7-14 days followed by;

(b) administering a contraceptively effective amount of an atrophizing progestin in combination with an estrogen in single daily doses for a period of 7-14 days;

(c) repeating steps (a) and (b) for a period of 21-90 days;

(d) withdrawing the administration for a period of about seven days; and

(e) repeating steps (a)-(d) continuously.

2. The regimen in accordance with claim 1 wherein the endometrial sparing progestin is selected from the group consisting of norgestimate and norethindrone;

the atrophizing progestin is selected from the group consisting of desogestrel, gestodene and levonorgestrel; and the estrogen is selected from the group consisting of ethinyl estradiol, mestranol, and 17-beta-estradiol.

3. The regimen in accordance with claim 2 wherein the endometrial sparing progestin is norgestimate.

4. The regimen in accordance with claim 2 wherein the atrophizing progestin is levonorgestrel.

5. The regimen in accordance with claim 2 wherein the atrophizing progestin is desogestrel.

6. The regimen according to claim 1 wherein the endometrial sparing progestin is norethindrone in a dosage range of about 0.065-2.0 mg per day; the atrophizing progestin is levonorgestrel in a dosage range of 0.050 - 0.250 mg per day; and the estrogen is ethinyl estradiol in a dosage range of about 0.020 - 0.050 mg per day.

7. The method of claim 1 wherein the regimen comprises:

a) administering a contraceptively effective amount of an endometrial sparing progestin in single daily doses for 10 days;

b) administering a contraceptively effective amount of an atrophizing progestin in single daily doses for 11 days;

c) withdrawing administration for seven days; and

d) repeating steps a)-c) continuously.

8. An extended use combination progestin and estrogen hormonal method and regimen for human contraception involving the sequential administration of two or more different progestational agents in combination with an estrogen comprising the steps of:

(a) administering a contraceptively effective amount of an endometrial sparing progestin in combination with an estrogen in single daily doses for a period of 7-14 days, followed by;

(b) administering a contraceptively effective amount of an atrophizing progestin in combination with an estrogen in single daily doses for a period of 7-14 days;

(c) repeating steps (a) and (b) for a period of 90 days;

(d) withdrawing the administration for a period of about seven days; and

(e) repeating steps (a)-(d) continuously.

9. The regimen in accordance with claim 8 wherein the endometrial sparing progestin is norethindrone in a dosage range of about 0.065-2.0 mg per day; the atrophizing progestin is levonorgestrel in a dosage range of 0.050-0.250 mg per day; and the estrogen is estradiol in a dosage range of about 0.020-0.050 mg per day.

10. A uniphasic combination progestin and estrogen hormonal method and regimen in accordance with claim 1 wherein the dosage of the estrogenic component is constant throughout the administration period and the relative dosages of the progestin components are constant throughout the administration period.

11. A uniphasic combination progestin and estrogen hormonal method and regimen in accordance with claim 10 wherein 0.035 mg of ethinyl estradiol is administered daily on days 1-21; 0.250 mg of norgestimate is administered daily on days 1-10; and 0.150 mg levonorgestrel is administered daily on days 11-21.

12. A biphasic combination progestin and estrogen hormonal method and regimen in accordance with claim 1 wherein the dosage of estrogenic component is constant throughout the administration period but the relative dosage of the progestin components are increased in a biphasic manner such that the relative dosage of the atrophizing progestin administered in step (b) is greater than the dosage of the endometrial sparing progestin administered in step (a).

13. A biphasic combination progestin and estrogen hormonal method and regimen in accordance with claim 12 wherein 0.035 mg of ethinyl estradiol is administered daily on days 1-21; 0.180 mg of norgestimate is administered daily on days 1-10; and 0.150 mg levonorgestrel is administered daily on days 11-21.

14. A triphasic combination progestin and estrogen hormonal method and regimen in accordance with claim 1

wherein the dosage of the estrogen component is constant throughout the administration period but the relative dosage of the progestin components is gradually increased in three phases throughout the administration period.

15. A triphasic combination progestin and estrogen hormonal method and regimen in accordance with claim 1 wherein 0.035 mg ethinyl estradiol is administered daily on days 1-21; 0.180 mg norgestimate is administered daily on days 1-7; 0.215 mg norgestimate is administered daily on days 8-14; and 0.150 mg levonorgestrel is administered daily on days 15-21.

16. A drug delivery system comprising a pharmaceutical package containing 21 separate dosage units, adapted for successive daily oral administration comprising:

7-14 dosage units, containing, in admixture with a pharmaceutical acceptable carrier, a combination of a contraceptively effective amount of an endometrial sparing progestin and an estrogen;

followed by 7-14 dosage units, containing, in admixture with a pharmaceutical acceptable carrier, a combination of a contraceptively effective amount of an atrophizing progestin and an estrogen, such that the total number of dosage units equals 21.

17. A drug delivery system in accordance with claim 16 optionally containing an additional 6-8 dosage units free of estrogen and progestin.

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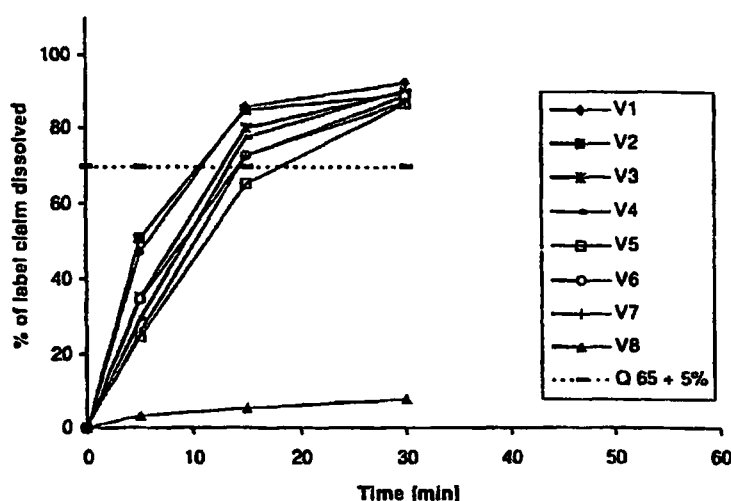
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[Continued on next page]

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



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

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PHARMACEUTICAL COMBINATION OF ETHINYLESTRADIOL AND DROSPIRENONE FOR USE AS A CONTRACEPTIVE

FIELD OF THE INVENTION

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

10 BACKGROUND OF THE INVENTION

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

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

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

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

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

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

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

SUMMARY OF THE INVENTION

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

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

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

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

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

BRIEF DESCRIPTION OF THE DRAWINGS

- The invention is further described with reference to the drawings in which
- 20 Fig. 1 is a graph showing the in vitro dissolution rate of drospirenone from tablet cores, V1-V7 being batches containing micronized drospirenone, and V8 being a batch containing macrocrystalline drospirenone;
- 25 Fig. 2 is a graph showing the in vitro dissolution rate of drospirenone from tablet cores, different lines representing different test batches;
- Fig. 3 is a graph showing the in vitro dissolution rate of drospirenone from film-coated tablets, different lines representing different test batches;
- 30 Fig. 4 is a graph showing the in vitro dissolution rate of ethinylestradiol from tablet cores, different lines representing different test batches; and
- Fig. 5 is a graph showing the in vitro dissolution rate of ethinylestradiol from film-coated 35 tablets, different lines representing different test batches.

DETAILED DISCLOSURE OF THE INVENTION

5 Drospirenone, which may be prepared substantially as described in, e.g., US 4,129,564 or 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 surprisingly been found that when drospirenone is provided in micronized form (so that particles of the active substance have a surface area of more than 10,000 cm²/g, and the following particle size distribution as determined under the microscope: not more than 2 particles in a given batch with a diameter of more than 30 µm, and preferably ≤ 20 particles with a diameter of ≥ 10 µm and ≤ 30 µm) in a pharmaceutical composition, rapid dissolution of the active compound from the composition occurs in vitro ("rapid dissolution" is defined as the dissolution of at least 70% over about 30 minutes, in particular at least 80% over about 20 minutes, of drospirenone from a tablet preparation containing 3 mg of drospirenone in 900 ml of water at 37°C determined by the USP XXIII Paddle Method using a USP dissolution test apparatus 2 at 50 rpm). Instead of providing the drospirenone in micronized form, it is possible to dissolve it in a suitable solvent, e.g. methanol or ethyl acetate, and spray it onto the surface of inert carrier particles followed by incorporation of the particles containing drospirenone on their surface in the composition.

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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.

With respect to ethinylestradiol which is also a sparingly soluble substance, though 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

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from a solution, e.g. in ethanol, onto the surface of inert carrier particles. This has the added advantage of facilitating a more homogenous distribution of the ethinylestradiol throughout the composition which might otherwise be difficult to obtain because ethinylestradiol is incorporated in extremely small amounts. When ethinylestradiol is

5 provided in micronized form, it preferably has the following particle size distribution as determined under the microscope: 100% of the particles have a diameter of $\leq 15.0 \mu\text{m}$, 99% of the particles have a diameter of $\leq 12.5 \mu\text{m}$, 95% of the particles have a diameter of $\leq 10.0 \mu\text{m}$, and 50% of the particles have a diameter of $\leq 3.0 \mu\text{m}$. Furthermore, no particle is larger than $20 \mu\text{m}$, and ≤ 10 particles have a diameter of $\geq 15 \mu\text{m}$ and $\leq 20 \mu\text{m}$.

10

To obtain a more rapid rate of dissolution, it is preferred to include carriers or excipients which act to promote dissolution of both active substances. Examples of such carriers and excipients include substances that are readily soluble in water such as cellulose derivatives, carboxymethylcellulose, hydroxypropyl cellulose, hydroxypropylmethyl

15 cellulose, gelled starch, gelatin or polyvinylpyrrolidone. In particular, it appears as though polyvinylpyrrolidone might be particularly helpful to promote dissolution.

The composition of the invention preferably comprises drospirenone in an amount corresponding to a daily dosage of from about 2.5 mg to about 3.5 mg, in particular about

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

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Apart from its ability to inhibit ovulation, the composition of the invention has been found to possess pronounced anti-androgenic properties and may therefore be used in the prevention or treatment of androgen-induced disorders, in particular acne. Such use may be independent from or concomitant with the use as a contraceptive disclosed above.

30 Furthermore, since drospirenone is an aldosterone antagonist, it has diuretic properties and is therefore suitable for counteracting the water-retentive properties of ethinylestradiol.

In a particular embodiment, the invention relates to a pharmaceutical preparation

35 consisting of a number of separately packaged and individually removable daily dosage

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

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

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

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

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

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

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

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

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

20

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

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

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

Alternatively, the present method comprises administering, on each day of at least 21 consecutive days, a daily dosage unit comprising a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about
10 0.01 to about 0.05 mg, followed by administering, on each day of 7 or less consecutive days, a daily dosage unit containing ethinylestradiol alone in an amount of from about 0.01 mg to about 0.05 mg.

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

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

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

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

A packaging unit comprising the daily dosage units described above may be prepared in a manner analogous to that of making other oral contraceptives. This may for instance be a conventional blister pack or any other form known for this purpose, for instance a pack comprising the appropriate number of dosage units (in this case at least 21, or for

5 particular applications, 28 or a multiple of 28) in a sealed blister pack with a cardboard, paperboard, foil or plastic backing and enclosed in a suitable cover. Each blister container may conveniently be numbered or otherwise marked, e.g. starting with the first of the at least 21 dosage units that contain the combination of drospirenone and ethinylestradiol, optionally followed by 7 or less empty blisters or by the 7 or less dosage units that contain

10 no active agent or that only contain ethinylestradiol (although the numbering may also start with the first of the 7 or less dosage units that only contain ethinylestradiol).

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

15 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

20 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

25 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 polacrylic acids or derivatives thereof. Transdermal formulations may also suitably contain one or

30 more substances that enhance absorption through the skin, such as bile salts or derivatives thereof and/or phospholipids. Suitable transdermal formulations may, for instance, be made in a manner analogous to that described in WO 94/04157 for 3-ketodesogestrel. Alternatively, transdermal formulations may be prepared according to a method disclosed in, e.g., BW Barry, "Dermatological Formulations, Percutaneous

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

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

EXPERIMENTAL

Example 1

10

Preparation of tablets containing drospirenone and ethinylestradiol

Tablet cores of the following composition

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

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

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

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

Example 2

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Dissolution of drospirenone from tablets

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

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

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

Example 3

25 *Dissolution rate of ethinylestradiol from tablets in vitro*

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

AF
150
150**Example 4**

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

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

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

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

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

25

Example 5

Contraceptive efficacy of formulations containing drospirenone and ethinylestradiol

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

35

At defined time points, selected central and peripheral parameters were investigated: LH, FSH, 17β -estradiol, progesterone, cervical score, "spinnbarkeit", fern phenomenon. Ovarian function was checked by ultrasound. In addition, SHBG, CBG, prolactine, total testosterone, androstenedione, DHEA-S and selected metabolic parameters (serum

5 glucose, triglycerides, cholesterol, HDL, LDL) were examined. Blood pressure, heart rate, body weight and cycle control were documented.

The results of the study showed that both LH and FSH were clearly suppressed with both trial preparations. Accordingly, the secretion of estradiol and progesterone were greatly

10 reduced over all three treatment cycles with the exception of 3 volunteers receiving the 2 mg drospirenone preparation. This result was, in principle, confirmed by the accompanying ultrasound examinations. Follicular ripening occurred in several cases with both trial preparations. Although three ovulations were diagnosed with the preparation containing 2 mg drospirenone (one of which was described as "equivocal" and the other

15 as a "tablet-taking error"), no differences were demonstrable statistically ($p > 0.05$) between the two trial preparations as regards the hormones LH, FSH, estradiol and progesterone, and the parameter "ovulation during the treatment cycles". In keeping with the hormones, cervical function was greatly limited and the "spinnbarkeit" and crystallisability of the cervical mucus was greatly reduced with both trial preparations.

20 Prolactin increased minimally and SHBG and CBG distinctly with both preparations. Triglycerides and HDL levels increased with both trial preparations, while LDL levels decreased. Total cholesterol was largely unchanged in both treatment groups. Oral glucose tolerance remained virtually unchanged or was slightly decreased. Testosterone, androstenedione and DHEA-S decreased minimally.

25

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

30

After three months' treatment, it was concluded:

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

CLAIMS

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

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

17. A preparation according to any of claims 10-16, wherein the at least 21 daily dosage units comprise drospirenone in an amount of from about 3.0 to about 3.5 mg and ethinylestradiol in an amount corresponding to from about 0.015 to about 0.03 mg.
- 5
18. A pharmaceutical preparation consisting of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 28 consecutive days, wherein at least 21 of said daily dosage units comprises a combination of drospirenone in an amount of from about 2
- 10 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg, and wherein 7 or less of said daily dosage units contain ethinylestradiol alone in an amount from about 0.01 to about 0.05 mg.
19. A preparation according to claim 18, wherein the number of daily dosage units
- 15 comprising the combination of drospirenone and ethinylestradiol is 21, 22, 23 or 24, and wherein the number of daily dosage units comprising ethinylestradiol alone is 7, 6, 5 or 4.
20. A preparation according to claim 18 or 19, wherein the at least 21 daily dosage units comprise drospirenone and ethinylestradiol in micronized form or sprayed from a solution
- 20 onto particles of an inert carrier.
21. A preparation according to any of claims 18-20, wherein the at least 21 daily dosage units comprise drospirenone in an amount of from about 2.5 mg to about 3.5 mg, in particular about 3 mg, and ethinylestradiol in an amount of from about 0.015 mg to about
- 25 0.04 mg, in particular from about 0.02 mg to about 0.03 mg.
22. A preparation according to any of claims 18-21, wherein the at least 21 daily dosage units comprise drospirenone in an amount of from about 3.0 to about 3.5 mg and ethinylestradiol in an amount corresponding to from about 0.015 to about 0.03 mg.
- 30
23. A method of inhibiting ovulation in a mammal, in particular a human, comprising administering, to said mammal, drospirenone in an amount in the range of from about 2 mg to about 4 mg of per day, together with ethinylestradiol in an amount of from about 0.01 mg to about 0.05 mg per day, said amounts being effective to inhibit ovulation in said
- 35 mammal.

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

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

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

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

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

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

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

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

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 00/01213

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/565 A61K31/585 A61P15/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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

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

☒ Patent family members are listed in annex.

* Special categories of cited documents:

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

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

Date of the actual completion of the international search

16 January 2001

Date of mailing of the international search report

23/01/2001

Name and mailing address of the ISA

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

Authorized officer

Gonzalez Ramon, N

INTERNATIONAL SEARCH REPORT

ST
766
166

International Application No
PCT/IB 00/01213

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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

-/-

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 00/01213

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 7-9

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

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 00/01213

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

Drosipirenona + Etinilestradiol
Ceyna
T70
JCO



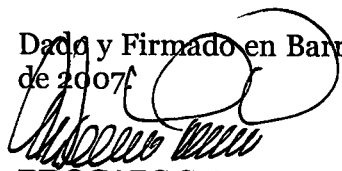
PODER ESPECIAL

Yo, **WALTER TANAKA TATEKAWA**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **LAURA CATALINA SILVA BARRERA**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 147399, poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 05 130.115, titulada "**COMPOSICIONES FARMACEUTICAS SOLIDAS QUE COMPRENDEN UNA COMBINACION DE DROSPIRENONA Y ETINILESTRADIOL Y UN AGENTE SUFACTANTE ADECUADO QUE PRESENTA UNA HOMogeneidad DE CONTENIDO Y VELOCIDAD DE DISOLUCIÓN ASEGURADA PARA LA DROGA NO MICRONIZADA Y PROCEDIMIENTO PARA PREPARAR DICHA COMPOSICIÓN Y USO DE ESTA COMPOSICIÓN PARA PREPARAR UN MEDICAMENTO** cuyo titular es **GADOR S.A.**, publicada en la gaceta No. 577 del 29 de Junio de 2007.

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 6 días del mes de Septiembre de 2007.


PROCAPS S.A.

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

Acepto:


LAURA CATALINA SILVA BARRERA
C.C. 52'455.803 de Bogotá
T.P.A. 147399 del C.S. de la J.

SEGUNDA NOTARIA SEGUNDA NOTARIA SEGUNDA NOTARIA SEGUNDA
 ADY ISABEL NAIMEN SEGURA
 NOTARIA SEGUNDA DEL CIRCULO DE BARRANQUILLA
 CERTIFICA
 Que la(s) firma(s) que aparece(n) en el documento que
 antecede se asemeja(n) a la(s) de Walter TONOKO
TONOKO
 Que aparece(n) registrada(s) en esta Notaria previa
 confrontación de la(s) misma(s).
 (Decreto 960/70)
 Barranquilla 19 de Sept de 2007
 LA NOTARIA _____

[Handwritten signature]



NOTARIA QUINCE (15) DEL CIRCULO DE BOGOTA

EL ANTERIOR ESCRITO FUE PRESENTADO
 PERSONALMENTE POR SU SIGNATARIO

Laura Catalina Silva Barrera

QUIEN SE IDENTIFICÓ CON LA C.C.

NUMERO 52 455 803

DE Bog Y T.P. DE ABOGADO

NO 747.399 DEL C.B.J.

RECONOCE EL CONTENIDO COMO CIERTO Y

MANIFIESTA QUE LA FIRMA FUE PUESTA
 POR EL

FIRMA: [Handwritten signature]

BOGOTA:

EL NOTARIO QUINCE:





***** 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
09*****

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

PROCAPS S.A.-----

NIT: 890.106.527-5.

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

C E R T I F I C A

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

C E R T I F I C A

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

C E R T I F I C A

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

C E R T I F I C A

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

C E R T I F I C A

Que por Escritura Pública No. 3,615 del 06 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el No. 67,218 del

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

FORMAS EFICIENTES 10015495-C FESR S.R. NIT. 890.321.151-0

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

PROCAPS S.A.-----

NIT: 890.106.527-5.

libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A

C E R T I F I C A

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

C E R T I F I C A

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

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

C E R T I F I C A

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

DENOMINACION O RAZON SOCIAL:

PROCAPS S.A.-----

SIGLA: PROCAPS.

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 890.106.527-5.

MATRICULA MERCANTIL: 24,802.

C E R T I F I C A

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



***** Pag. 2
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
09*****

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

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

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

C E R T I F I C A

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

C E R T I F I C A

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

***** 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.

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

C E R T I F I C A

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

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad correspondera a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva.

La sociedad tendra un Presidente , quien ejercera la representacion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. Ejercer la Representacion Legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, disistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la socieda todo acto o contrato cuya cuantia sea igual o inferior al equivalente

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



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PROCAPS S.A.-----

NIT: 890.106.527-5.

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

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NIT: 890.106.527-5.

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

C E R T I F I C A

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

PROCAPS S.A.

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

PROCAPS S.A.

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

CLASE:

JUNTA DIRECTIVA

Principales

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

Suplentes

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

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Presidente.	

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



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NIT: 890.106.527-5.

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
Revisor Fiscal Ppal.	
Vargas Pertuz Ana Isabel	CC.*****32,696,645

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

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

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

PROCAPS S.A.-----

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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, otorgada 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 continuacion se indican en razon de su cargo en la sociedad: 1.-Se confiere 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 o solicitudes de informacion de las autoridades tributarias, aduaneras o cambiarias, en los ordenes Distrital, Departamental y Nacional. 2.-Se confiere 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 dia que se realice la respectiva transaccion. GUPO A: CLAUDIA TANGARIFE CASTILLO C.C. No. 41.660.293. BRUPO B: WALTER TANAKA TATEKAWA C.C. No. 16.251.923, 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 requerira 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 contencioso administrativas y de tutela, transigir, conciliar, recibir en nombre de la sociedad desistir, sustituir y reasumir este mandato. Para la celebracion de cualquier acuerdo conciliatorio o transaccional, judicial o extrajudicial, cualquiera que sea su cuantia, los Apoderados deberan aportar la autorizacion escrita del Representante Legal de la sociedad. Los Apoderados podran presentar solicitudes de devolucion y/o

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



***** Pag. 5
C A M A R A D E C O M E R C I O
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PROCAPS S.A.-----
NIT: 890.106.527-5.

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, inscrito 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 Barranquilla, para que en su nombre y representacion de la sociedad suscriba 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 ESPECIAL 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 Exterior y/o cualquier entidad del Estado que haga sus veces. En consecuencia, el Sr. MARLON TATIS PAREDES, podra suscribir en representacion de PROCAPS S.A. declaraciones, reportes y cualquier tipo de documentos 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, bajo el No. 2.753 del libro respectivo consta que RUBEN MINSNSKI GONTOVNIK, C.C. 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 socia-

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

10015405-C
FORMAS EFICIENTES
NIT. 890.321.151-0
PROCAPS S.A.

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

les. Por lo anterior, el señor ANTONIO VARELA DIAZ, queda facultado para firmar las declaraciones comabiarías y demás documentos relacionados con las declaraciones, notificaciones, aportar y solicitar las pruebas que sean necesarias, desistir en general a realizar todo acto necesario de tal forma que pueda cumplir con el mandato dado.--

C E R T I F I C A

Que según documento privado del 22 de Febrero de 2005, inscrito en esta Cámara 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 actúa 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 representación de PROCAPS S.A., suscriba declaraciones aduaneras, reportes y cualquier tipo de documentos relacionados con los trámites o registros de comercio exterior ante la dirección 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 información de las autoridades aduaneras en los órdenes distrital, departamental y nacional.-----

C E R T I F I C A

Que por Escritura Pública No. 2,011 del 10 de Octubre de 2006, otorgada en la Notaría 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Dic/bre de 2006 bajo el No. 3,183 del libro respectivo,-----
Consta que RUBEN MINSKI GONTOVNIK CC.No.7.463.928, quien manifiesto que en su condición 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 dólares de los Estados Unidos de América (US\$800.000.00), ---- liquidados a la tasa representativa del mercado vigente en el día que se realice la respectiva transacción. Grupo A: IVAN VILLAREAL CAMACHO CC.No.91.201.749. FERNANDO RINCON RIVERA CC.No.79.484.187. CLAUDIA TANGARIFE CASTILLO CC.No.41.660.293. Grupo B. WALTER TANAKA TATEKAWA CC.No.16.251.923. CARMEN ALICIA FLOREZ DE LA ROTA ----- CC.No.22.434.044. RICARDO DORADO HURTADO CC.No.79.715.772.-----

C E R T I F I C A

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

C E R T I F I C A

Que su última Renovación fue el: 20 de Marzo de 2007.

La información sobre embargos de establecimiento se suministra en

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

03-13010994 024802 PROCAPS S.A.
Barranquilla, 07 de Sep/bre de 2007

Hr:15:32:41

No. 11571748



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C A M A R A D E C O M E R C I O
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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

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

m. fajon

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 78,342
FECHA : SEPTIEMBRE 27 DE 2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-130115- -00006-0000

Fecha: 2007-09-27 13:44:32 Dep. 2020 NUECREACIONE
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Act 400 OPOSIOBSERVTER Folios: 72

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
PHARM S.A.	CONSIGNACION	BANCO POPULAR	050-00110-6	68973420	31/07/2007	768,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
12		MARCAS Y LEHAS COMERCIALES	256,000.00
		TOTAL :	\$ 256,000.00

SON: DOSCIENTOS CINCUENTA Y SEIS MIL PESOS

ISABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.