

SUPERINDUSTRIA Y COMERCIO
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 Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Folios: 105

Doctor,

JAIRO RUBIO ESCOBAR

Superintendente de Industria y Comercio

E. S. D.

Referencia : Expediente N° 00-65489

Asunto : Remisión de información a la solicitud de patente de Invención titulada "UNA COMPOSICIÓN FARMACÉUTICA PARA SER USADA COMO ANTICONCEPTIVO".

Solicitante: SCHERING AKTIENGESELLSCHAFT.

Yo, Oscar Guillermo Pinto García, obrando en mi propio nombre y representación, con el animo de colaborar con esa Entidad en la decisión que sobre la patentabilidad de la solicitud de la referencia se tomará, me permito solicitarle, muy respetuosamente, dar curso a la siguiente información relativa al arte anterior relevante para que sea tomado en cuenta en el estudio de patentabilidad de la solicitud de patente de Invención de la referencia.

1. PETICIÓN.

Ruego al Señor Superintendente, NEGAR, en los términos de artículo 48 de la Decisión 486 de 2000 de la CAN, la Solicitud de Patente de Invención denominada "UNA COMPOSICIÓN FARMACÉUTICA PARA SER USADA COMO ANTICONCEPTIVO", cuyo solicitante es SCHERING AKTIENGESELLSCHAFT, con base en los siguientes hechos y fundamentos de derecho, relacionados con el

incumplimiento de los requisitos fundamentales exigidos para la concesión de Patentes de Invención, según la legislación vigente.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 31 de agosto de 2000, reivindicando prioridad bajo EP 99202826.6 del 31 de agosto de 1999 y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 520, del 27 de septiembre de 2002, bajo el N° de publicación NP. 771 (página 252).

2.2. La solicitud colombiana 00-65489 objeto de la presente remisión, comprende una composición farmacéutica, caracterizada por comprender, como un primer agente activo, 6beta, 7beta; 15beta, 16beta-dimetilen-3-oxo-17alfa-pregn-4-en-21, 17 - carbolactona (drospirenona) en una cantidad correspondiente a una dosis diaria, a ser administrada con la composición, de desde aproximadamente 2 mg a aproximadamente 4 mg, y, como un segundo agente activo, 17a-etinilestradiol (etinilestradiol) en una cantidad correspondiente a una dosis diaria de desde aproximadamente 0,01 mg a aproximadamente 0,05 mg, conjuntamente con uno o más soportes o excipientes farmacéuticamente aceptables. De igual forma se refiere a una preparación farmacéutica, caracterizada por consistir de un número de unidades de dosificación diaria colocadas en una unidad de empaque, empaquetadas separadamente y separables individualmente, y provistas para la administración oral durante un periodo de 21 días consecutivos, comprendiendo dichas unidades de dosificación diaria una combinación de drospirenona en una cantidad de desde aproximadamente 2 mg a aproximadamente 4 mg y etinilestradiol en una cantidad de desde aproximadamente 0,01 a aproximadamente 0,05 mg. De igual forma reivindica una preparación

farmacéutica caracterizada por consistir de un número de unidades de dosificación diaria colocadas en una unidad de empaque, empaquetadas separadamente y separables individualmente y provistas para la administración oral durante un periodo de al menos 28 días consecutivos, en donde al menos 21 de dichas unidades de dosificación diaria comprenden una combinación de drospirenona en una cantidad de desde aproximadamente 2 mg a aproximadamente 4 mg y etinilestradiol en una cantidad de desde aproximadamente 0,01 a aproximadamente 0,05 mg, y en donde 7 ó menos de dichas unidades de dosificación diaria contienen sólo etinilestradiol en una cantidad de desde aproximadamente 0,01 a aproximadamente 0,05 mg. Incluye también, un método para inhibir ovulación en un mamífero, en particular en un humano, caracterizado por comprender administrar, a dicho mamífero, drospirenona en una cantidad en la gama de desde aproximadamente 2 mg a aproximadamente 4 mg por día, conjuntamente con etinilestradiol en una cantidad de desde aproximadamente 0,01 mg a aproximadamente 0,05 mg por día, siendo dichas cantidades efectivas para inhibir ovulación en dicho mamífero; así como un método para promover una disolución rápida de drospirenona de una forma de dosificación unitaria para administración oral, estando el método caracterizado por comprender proveer drospirenona, en dicha forma de dosificación unitaria, en forma micronizada, o pulverizada desde una solución sobre las partículas de un soporte inerte mezclado con uno o más excipientes farmacéuticamente aceptables que promueven la disolución de la drospirenona.

2.3. El arte anterior revela los siguientes documentos relevantes sobre esta materia, de los cuales:

- D1: US4129564, Publicada el 12 de diciembre de 1978.

- D2: "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. Publicada en 1995. The Endocrine Society.
- D3: EP0253607, Publicado el 20 de enero de 1988.
- D4: US5569652, Publicada el 29 de octubre de 1996.
- D5: US5756490, Publicada el 26 de mayo de 1998.
- D6: WO9804267, Publicada el 5 de febrero de 1998.
- D7: EP0956024(B1), Publicada el 5 de febrero de 1998.
- D8: US5583129, Publicada el 10 de diciembre de 1996.
- D9: WO9701342 (US6027749), Publicada el 16 de enero de 1997.

2.4. El arte previo a la solicitud Colombiana se remonta hacia 1978, donde se revela un procedimiento para la preparación, así como la descripción del gestageno de drospirenona (DRSP), se remite a la publicación del 12 de diciembre de 1978, en el documento D1 (Véase Reivindicaciones del D1). Los estudios sobre los efectos por dosificación oral que contienen drospirenona en contraceptivos, se remontan hacia 1995, tal y como lo define el documento D2 (Véase Página 1816 y siguientes del D2). De igual forma, el uso de estrógenos tales como el etinilestradiol (EE) en tratamientos contraceptivos para mujeres pre-menopáusicas se evidencia en el documento D3 (Véase resumen y descripción del D3), desde 1988.

2.5. Ahora bien, una combinación de un gestageno tal como drospirenona (dihidrospirenona, DRSP) y un estrógeno tal como etinilestradiol (17 α -etinilestradiol) se revela claramente en el documento D4 (Véase Descripción y reivindicaciones 12 y 27 especialmente). De hecho, en la cláusula 27 del documento D4 se evidencia, que para 1996, el arte definía "27. Un método según la reivindicación 11, donde

dicha cantidad efectiva de dihidrospironona es 0.5-50 mg por día y donde dicha cantidad efectiva de un compuesto estrogénico es una cantidad equivalente a 0.02-0.04 mg de 17.alpha.-ethynylestradiol por día. (el destacado y traducción son nuestros). Bajo la óptica de este documento D4, específicamente bajo lo que dicta sus cláusulas 12 y 27, es claro que lo referenciado en el documento Colombiano, CARECE DE NOVEDAD, pues su referencia ya era conocida en la técnica a la fecha de prioridad de 1999, desde 1996. De hecho, las proporciones de la solicitud Colombiana están dentro de las proporciones reveladas en las cláusulas 12 y 27 del documento D4, donde:

SOLICITUD COLOMBIANA	DOCUMENTO D4.
Prioridad del 31 de agosto de 1999	Publicado el 26 de mayo de 1998.
Composición farmacéutica, caracterizada por comprender, una combinación de: Drospironona: <u>2 a 4 mg</u> , por día. y, 17a-etinilestradiol: <u>0,01 a 0,05 mg</u> . por día.	Composición farmacéutica, caracterizada por comprender, una combinación de: Drospironona: <u>0,5 a 50 mg</u> , por día. y, 17a-etinilestradiol: <u>0,5 a 4,0 mg</u> (Reivindicación 12) por día. o, 17a-etinilestradiol: <u>0,02 a 0,04 mg</u> . (Reivindicación 27) por día

2.6. De igual forma, revisando el contenido del documento D5 (Véase capítulo reivindicatorio, especialmente cláusulas 1 y 3), éste revela una preparación en combinación farmacéutica con dos componentes que son físicamente separados en una unidad de empaquetamiento para la administración oral tiempo-secuencial que consiste en varias unidades de dosificación diaria físicamente separadas e individualmente trasladables que como ingrediente activo hormonal en la unidad

del empaquetamiento, comprende un primer componente de la hormona que contiene en combinación una preparación de estrógeno tal como 17a-etinilestradiol y una preparación de gestageno tal como drospirenona y un segundo componente de hormona que contiene una preparación de estrógeno tal como 17a-etinilestradiol únicamente, donde el primer componente de la hormona comprende 23 o 24 unidades diarias y el segundo componente de la hormona comprende 4 a 10 unidades diarias y el número total de las unidades diarias son iguales al número total de días del ciclo deseado, por lo menos 28 días (Véase reivindicaciones 1 y 2). Ahora bien, las proporciones propuestas, reveladas en la reivindicación 3 y siguientes del D5, se refieren a que en el primer componente comprende de 0.015 a 0.025 mg de 17a-etinilestradiol y de 1.0 a 3.0 mg de drospirenona; y, en el segundo componente comprende de 0.002 a 0.04 mg de 17a-etinilestradiol, preferiblemente 0.01 a 0.025 mg. Al leer lo propuesto aquí, en este documento D5, claramente se percibe su estrecha igualdad con lo definido en el capítulo reivindicatorio de la solicitud Colombiana. Véamos:

SOLICITUD COLOMBIANA	DOCUMENTO D5.
Prioridad del 31 de agosto de 1999	Publicada el 29 de octubre de 1996
Una preparación en combinación farmacéutica con dos componentes que son físicamente separados donde el primero comprende:	Una preparación en combinación farmacéutica con dos componentes que son físicamente separados donde el primero comprende:
0.01 a 0.05 mg de 17a-etinilestradiol y	0.015 a 0.025 mg de 17a-etinilestradiol y
de 2.0 a 4.0 mg de drospirenona, por día, con al menos 21 dosis,	de 1.0 a 3.0 mg de drospirenona, por día, con 23 o 24 dosis,
y, el segundo comprende	y, el segundo comprende
17a-etinilestradiol: <u>0.01 a 0.05 mg.</u> por día, con 7 o menos dosis;	17a-etinilestradiol: <u>0.002 a 0.04 mg.</u> por día, con 3 a 10 dosis;
y,	y,
Provistas para la administración oral de al	Provistas para la administración oral de al menos 28

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menos 28 días.	días.
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Así las cosas, este documento D5, específicamente a la luz lo que dicta sus cláusulas 1 a 13 del D5, define con anterioridad lo referenciado en el documento Colombiano, de tal forma que lo que pretende esta solicitud, CARECE DE NOVEDAD, pues su referencia ya era conocida en la técnica a la fecha de prioridad de 1999, desde 1998. De hecho, el arte anterior D5, define también la solución propuesta de empaque individual y separado de dos componentes; que el primero comprenda la combinación de drospirenona y 17 α -etinilestradiol y el segundo sólo 17 α -etinilestradiol; que las proporciones de cada componente están dentro de los rangos de la solicitud Colombiana; y, que las dosis y la administración están dentro de los rangos de la solicitud Colombiana.

2.7. De igual forma, la combinación reivindicada en la solicitud Colombiana, referida a 17 α -etinilestradiol y drospirenona (EE/DRSP) en forma microionizada no es NOVEDOSA con base en lo que dictan los documentos D6 y D7. En estos documentos se define claramente (Véanse resúmenes) proporciones para un método de anticoncepcionismo que comprende una administración de una combinación de un gestageno tal como 250 μ g a 4 mg drospirenona y un estrógeno a una dosificación diaria equivalente a 10 a 20 μ g 17 α -etinilestradiol durante 23 a 25 días que empiezan en día 1 del ciclo menstrual. Adicionalmente define que la misma dosificación del gestageno (drospirenona) en combinación con el estrógeno se administra en cada uno de los 23 a 25 días, seguido por la administración del estrógeno a una dosificación diaria equivalente a 5 a 15 μ g de 17 α -etinilestradiol durante 3 a 5 días; en donde la misma dosificación del estrógeno se administra en cada uno de los 3 a 5 días; tal que el número de días de administración del gestageno (drospirenona) en combinación de estrógeno (17 α -etinilestradiol) más el

número de días de administración de estrógeno (17a-etinilestradiol), es igual a 28 por el ciclo menstrual. Por lo tanto, es posible concluir que bajo estos documentos D6 y D7, el documento Colombiano CARECE DE NOVEDAD, pues su referencia ya era conocida en la técnica a la fecha de prioridad de 1999, desde 1998.

2.8. En relación al documento D8, este define con anterioridad un método para inducir el anticoncepcionismo que comprende administrar un estrógeno de 0.015 a 0.020 mg de 17a-etinilestradiol y un gestageno de 0.1 a 0.3 mg de drospirenona, para la administración durante 23 o 24 días, durante el ciclo menstrual, seguido por 5 o 4 dosis de píldoras sin efecto, para un total de 28 días para el ciclo de administración. A partir de este documento D8 y en combinación con los documentos D1, D2 y D3, es posible deducir lo contemplado en la solicitud Colombiana, dado que cualquier persona versada en la materia puede llegar de manera evidente a la solución propuesta. Por lo tanto, es posible concluir que bajo este documento D8 y en combinación con los documentos D1, D2 y D3, el documento Colombiano CARECE DE NIVEL INVENTIVO.

2.9. Ahora bien, el documento D9 define una preparación farmacéutica de dos fases para anticoncepcionismo hormonal que contiene 30 unidades diarias donde en su primera fase, comprende drospirenona en combinación con 17a-etinilestradiol y, en la segunda fase sólo comprende como el ingrediente activo hormonal un 17a-etinilestradiol, en donde la primera fase comprende un mínimo de 25 y un máximo de 77 unidades diarias y la segunda fase comprende 5, 6 o 7 unidades diarias, y en donde el número total de unidades diarias es igual al número total de días del ciclo deseado de un mínimo de 30 y un máximo de 84 días. Así las cosas, este documento D9, específicamente a la luz lo que dicta sus cláusulas y el resumen, define con anterioridad lo referenciado en el documento Colombiano, de tal forma que lo que pretende esta solicitud, CARECE DE NOVEDAD, pues su

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referencia ya era conocida en la técnica a la fecha de prioridad de 1999, desde 1997. De hecho, el arte anterior D9, define también la solución propuesta de dos fases; donde la primera comprenda la combinación de drospirenona y 17a-etinilestradiol y la segunda fase sólo 17a-etinilestradiol; que las proporciones de cada componente están dentro de los rangos de la solicitud Colombiana; y, que las dosis y la administración están dentro de los rangos de la solicitud Colombiana.

2.10. Adicionalmente, vale la pena advertir que en materia de dosis y en materia de empaque individual y separado de dos componentes para la administración en 28 días, a todas luces no comprende el requisito de APLICACIÓN INDUSTRIAL, pues como tal, según el Artículo 19, de la Decisión 486 de la CAN y ello NO PUEDE SER PRODUCIDO O UTILIZADO EN CUALQUIER TIPO DE INDUSTRIA. Por lo tanto, la Solicitud Colombiana, también carecería de APLICACIÓN INDUSTRIAL.

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

2.11.1. CARECE DE NOVEDAD: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *“Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.”*. A la fecha de prioridad, 31 de agosto de 1999, ya era conocido, pues como se demostró, era parte del arte anterior la materia sobre la cual busca protección en el capítulo reivindicatorio con base en los documentos D4, D5, D6, D7 y D9 .

2.11.2. 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 presentación, 31 de agosto de 1999, el documento D8 en combinación con los documentos D1, D2 y D3, es posible deducir la combinación referida a 17a-etinilestradiol y drospirenona (EE/DRSP) en forma microionizada y sus proporciones, la forma de administración y los periodos reivindicados.

2.11.3. CARENCIA DE APLICACIÓN INDUSTRIAL Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 19.- “Se considerará que una invención es susceptible de aplicación industrial, cuando su objeto pueda ser producido o utilizado en cualquier tipo de industria, entendiéndose por industria la referida a cualquier actividad productiva, incluidos los servicios”, y lo propuesto en el capítulo reivindicatorio en materia de dosis y en materia de empaque individual y separado de dos componentes para la administración en 28 días, NO PUEDE SER PRODUCIDO O UTILIZADO EN CUALQUIER TIPO DE INDUSTRIA.. Por lo tanto, la Solicitud Colombiana, también carecería de APLICACIÓN INDUSTRIAL

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 los TRES requisitos de patentabilidad.

- 2.13. Por consiguiente, si se concede el registro solicitado se induciría al monopolio de un producto que no cumple con los requisitos primordiales exigidos por la mencionada Decisión 486.
- 2.14. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente remisión y negar el registro Patente de invención denominada "UNA COMPOSICIÓN FARMACÉUTICA PARA SER USADA COMO ANTICONCEPTIVO", cuyo solicitante es SCHERING AKTIENGESELLSCHAFT.

3. PRUEBAS

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

- D1: US4129564, Publicada el 12 de diciembre de 1978.
- D2: "Effects Of A New Oral Contraceptive Containing An Antimineralocorticoid Progestogen, Drospirenone, On The Renin-Aldosterone System, Body Weight, Blood Pressure, Glucose Tolerant, And Lipid Metabolism", Journal of Clinical Endocrinology and Metabolism. Publicada en 1995. The Endocrine Society.
- D3: EP0253607, Publicado el 20 de enero de 1988.
- D4: US5569652, Publicada el 29 de octubre de 1996.
- D5: US5756490, Publicada el 26 de mayo de 1998.
- D6: WO9804267, Publicada el 5 de febrero de 1998.
- D7: EP0956024(B1), Publicada el 5 de febrero de 1998.

- D8: US5583129, Publicada el 10 de diciembre de 1996.
- D9: WO9701342 (US6027749), Publicada el 16 de enero de 1997.

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 48 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.

5. ANEXOS

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

- D1: US4129564, Publicada el 12 de diciembre de 1978.
- D2: *"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. Publicada en 1995. The Endocrine Society.
- D3: EP0253607, Publicado el 20 de enero de 1988.
- D4: US5569652, Publicada el 29 de octubre de 1996.
- D5: US5756490, Publicada el 26 de mayo de 1998.
- D6: WO9804267, Publicada el 5 de febrero de 1998.
- D7: EP0956024(B1), Publicada el 5 de febrero de 1998.

- D8: US5583129, Publicada el 10 de diciembre de 1996.
- D9: WO9701342 (US6027749), Publicada el 16 de enero de 1997.
- Poder para actuar a nombre de mi representada.

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 de abogado situadas en la calle 119ª N° 53-99 de esta ciudad de Bogotá.

Señor Superintendente,



OSCAR GUILLERMO PINTO GARCÍA

C.C. 79420100 BTP

United States Patent [19]

Wiechert et al.

[11] 4,129,564

[45] Dec. 12, 1978

[54] SPIROLACTONES

[75] Inventors: Rudolf Wiechert; Dieter Bittler;
Ulrich Kerb; Jorge Casals-Stenzel;
Wolfgang Losert, all of Berlin, Fed.
Rep. of Germany

[73] Assignee: Schering, A.G. Patentabteilung,
Berlin, Fed. Rep. of Germany

[21] Appl. No.: 850,524

[22] Filed: Nov. 11, 1977

[30] Foreign Application Priority Data

Nov. 16, 1976 [DE] Fed. Rep. of Germany 2652761

[51] Int. Cl.² A61K 31/58; C07J 1/00

[52] U.S. Cl. 260/239.57; 424/241

[58] Field of Search 260/239.57;
/Machine Searched Steroids

[56] References Cited

U.S. PATENT DOCUMENTS

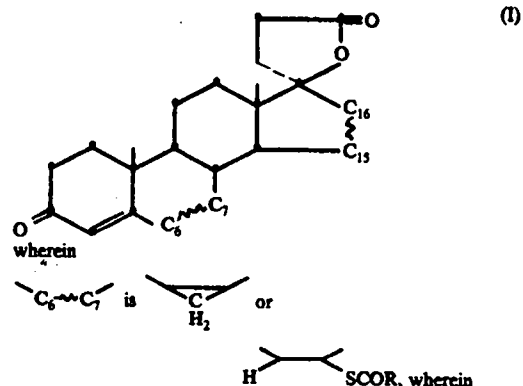
3,257,390 6/1966 Patchett 260/239.55
3,900,467 8/1975 Irmischer et al. 260/239.57

Primary Examiner—Elbert L. Roberts
Attorney, Agent, or Firm—Millen & White

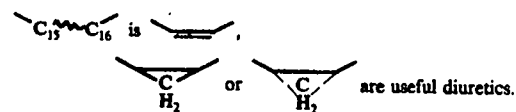
[57]

ABSTRACT

New spirolactones of the formula



R is a lower alkyl of up to 5 carbon atoms, and



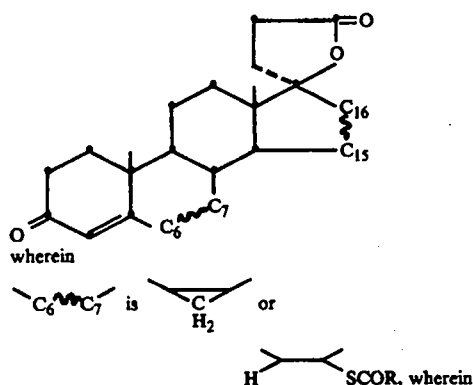
19 Claims, No Drawings

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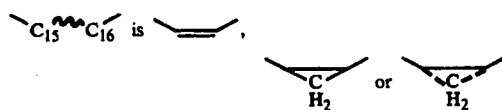
SPIROLACTONES

SUMMARY OF THE INVENTION

The present invention provides novel spirolactones of Formula I



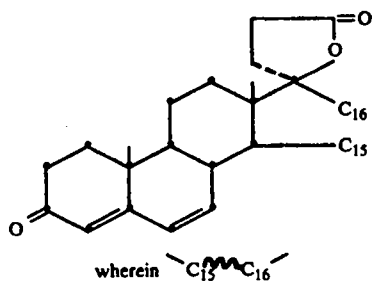
R is a lower alkyl of up to 5 carbon atoms, and



Lower alkyl residues include branched and unbranched groups, preferably methyl, ethyl and n-propyl.

DETAILED DISCUSSION

The spirolactones of Formula I can be prepared by conventionally introducing the methylene group or the thiacyl group into the Δ^6 -unsaturated spirolactones of Formula II



is as defined above.

The methylene group is introduced into the compounds of Formula II in accordance with conventional methods, for example, by reaction of the compounds with dimethyl sulfoxonium methylide in an aprotic solvent, such as dimethyl sulfoxide, dimethylformamide, dioxane, or a mixture of dimethyl sulfoxide and tetrahydrofuran. See for reference, E. J. Corey and M. Chaykovsky, J. Am. Chem. Soc. 84 (1962)867 and ibid. 84 (1962)3782.

This process is advantageously conducted at 20°-40° C. under a protective gas atmosphere, such as nitrogen.

The dimethyl sulfoxonium methylide is suitably prepared by reaction of trimethyl sulfoxonium iodide or chloride with a base, such as sodium hydride, sodium

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hydroxide, potassium tert-butyrate, or sodium methylate.

The dimethyl sulfoxonium methylide is prepared in a conventional manner (see for reference, L. F. Fieser & M. Fieser, Reagents for Organic Synthesis, J. Wiley & Sons, Inc., N.Y., 1967, p. 315).

The thiacyl group is also introduced into the compounds of Formula II in accordance with known procedures. Especially suitable is the reaction of the compounds with the corresponding thio acid in the presence of a protonic solvent, such as methanol or ethanol, optionally in a mixture thereof with water, while heating. For reference, see process described in U.S. Pat. No. 3,013,102.

The preferred temperature range is that from above room temperature up to the boiling point of the reaction mixture.

It is also possible to conduct the thiacylation without a solvent.

The three starting materials of Formula II which are required for preparation of all compounds of Formula I in accordance with the foregoing procedures, i.e.,

25	Starting Material	C_6C_7
	3-oxo-4,6,15-androstatriene-[17-(β -1')-spiro-5']perhydrofuran-2'-one	
30	15 α ,16 α -methylene-3-oxo-4,6-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one	
35	15 β ,16 β -methylene-3-oxo-4,6-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one	

can be prepared as follows:

40 3-oxo-4,6,15-androstatriene-[17-(β -1')-spiro-5']perhydrofuran-2'-one

(II) 20.0 g. of 3 β -hydroxy-5,15-androstadiene-17-one is combined in 280 ml. of absolute tetrahydrofuran with 4.34 g. of freshly pressed lithium wire. Then, 36 ml. of 1-bromo-3-dimethoxypropane is added dropwise under ice cooling within 30 minutes. After 1.5 hours of agitation at ice-bath temperature, the mixture is filtered off from the unreacted lithium, and the filtrate is stirred into ice water. The precipitate is filtered off, washed with water, and taken up in methylene chloride.

After drying and evaporation, the residue is chromatographed on silica gel, thus obtaining 19.9 g. of 17 α -(3'-dimethoxypropyl)-5,15-androstadiene-3 β ,17 β -diol in the form of an oil.

19.9 g. of 17 α -(3'-dimethoxypropyl)-5,15-androstadiene-3 β ,17 β -diol is combined in 500 ml. of acetone under ice cooling with 1.0 g. of p-toluenesulfonic acid and stirred for 15 minutes under cooling. The mixture is then introduced under agitation into ice water which contains sodium bicarbonate; the precipitate is filtered off, washed, and taken up in methylene chloride. After drying and evaporation, 9.2 g. of crude 3 β -hydroxy-5,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'- ξ -methyl ether is obtained in the form of an oil.

19.2 g. of 3 β -hydroxy-5,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'- ξ -methyl ether is combined in 394 ml. of absolute toluene and 39.4 ml. of cyclohexanone with 3.94 g. of aluminum isopropylate in 40 ml. of

absolute toluene and heated for 45 minutes under gradual distillation. The mixture is then diluted with methylene chloride, washed with dilute sulfuric acid and water, dried, and evaporated. The residue is chromatographed on silica gel, thus obtaining 17.5 g. of 3-oxo-4,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'- ξ -methyl ether in the form of an oil.

UV: $\epsilon_{239} = 16,200$.

17.5 g. of 3-oxo-4,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'- ξ -methyl ether is combined in 350 ml. of acetone under ice cooling with 35 ml. of chromosulfuric acid (prepared from 267 g. of CrO_3 , 400 ml. of water, and 230 ml. of concentrated sulfuric acid, replenished with water to obtain 1 liter); the mixture is stirred for 30 minutes under cooling in an ice bath. The mixture is then stirred into ice water, the precipitate is filtered off, washed with water, and taken up in methylene chloride. After drying and evaporation, the residue is chromatographed on silica gel, thus obtaining 11.8 g. of 3-oxo-4,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one. A sample recrystallized from diisopropyl ether/acetone melts at 189.5°-191.5° C.

UV: $\epsilon_{240} = 17,300$.

10.0 g. of 3-oxo-4,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one is combined in 100 ml. of absolute dioxane with 10 ml. of triethyl orthoformate and 10 ml. of dioxane/concentrated sulfuric acid (produced from 13.5 ml. of absolute dioxane and 0.48 ml. of concentrated sulfuric acid). The mixture is stirred for 30 minutes at room temperature, combined with 2 ml. of pyridine, and diluted with ether. The ether phase is washed with water, dried, and evaporated. The residue is triturated with pyridine-containing methanol, the thus-separated crystals are vacuum-filtered. Yield: 8.9 g. of 3-ethoxy-3,5,15-androstatriene-[17(β -1')-spiro-5']perhydrofuran-2'-one, m.p. 153.5°-159° C.

UV: $\epsilon_{240} = 19,800$.

8.9 g. of 3-ethoxy-3,5,15-androstatriene-[17(β -1')-spiro-5']perhydrofuran-2'-one is dissolved in 201 ml. of acetone, cooled in an ice bath, and combined with 1.38 ml. of pyridine, 6.36 g. of sodium acetate, and 63.6 ml. of water. Then, 4.72 g. of N-bromosuccinimide is added thereto, and 6.36 ml. of acetic acid is added dropwise over a period of 15 minutes. The mixture is further stirred for 45 minutes under ice cooling, diluted with ether, and washed neutral with water. After drying and evaporation, 10.35 g. of 6 β -bromo-3-oxo-4,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one is obtained in the form of an oil.

UV: $\epsilon_{245} = 12,700$.

10.35 g. of 6 β -bromo-3-oxo-4,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one is stirred in 103.5 ml. of dimethylformamide with 4.67 g. of lithium carbonate and 5.37 g. of lithium bromide for 18 hours at 100° C. The mixture is then introduced into ice water under agitation, the precipitate is filtered off, washed with water, and taken up in methylene chloride. After drying and evaporation, the residue is chromatographed. After recrystallization from diisopropyl ether/acetone, 6.5 g. of 3-oxo-4,6,15-androstatriene-[17(β -

1')-spiro-5']perhydrofuran-2'-one is obtained, m.p. 182.5°-184.5° C.

UV: $\epsilon_{284} = 27,100$.

15 α ,16 α -methylene-3-oxo-4,6-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one

15 g. of 3 β -hydroxy-15 α ,16 α -methylene-5-androstene-17-one (produced, for example, according to DOS [German Unexamined Laid-Open Application] 2,109,555) is combined in 150 ml. of absolute tetrahydrofuran under ice cooling with 3.6 g. of lithium and thereafter 30 ml. of 1-bromo-3-dimethoxypropane is added dropwise within 30 minutes. After agitation for 2.5 hours at ice bath temperature, the mixture is separated from the unreacted lithium, and the filtrate is stirred into ice water. The thus-obtained precipitate is filtered off, washed with water, and taken up in methylene chloride. After drying and evaporation, the residue is chromatographed on silica gel, thus obtaining 16.8 g. of 17 α -(3'-dimethoxypropyl)-15 α ,16 α -methylene-5-androstene-3 β ,17 β -diol. A sample recrystallized from diisopropyl ether/acetone melts at 153°-159° C.

16.5 g. of 17 α -(3'-dimethoxypropyl)-15 α ,16 α -methylene-5-androstene-3 β ,17 β -diol is agitated in 410 ml. of 70% acetic acid for 18 hours at room temperature. The mixture is then stirred into ice water, and the thus-obtained precipitate filtered off, taken up in chloroform, and washed with sodium bicarbonate solution and water. After drying and evaporation, the residue is chromatographed on silica gel, thus obtaining 11.5 g. of 3 β -hydroxy-15 α ,16 α -methylene-5-androstene-[17(β -1')-spiro-5']perhydrofuran-2'- ξ -ol. A sample recrystallized from diisopropyl ether/acetone melts at 194°-202° C.

10.5 g. of 3 β -hydroxy-15 α ,16 α -methylene-5-androstene-[17(β -1')-spiro-5']perhydrofuran-2'- ξ -ol is combined in 210 ml. of absolute toluene with 21 ml. of cyclohexanone and 2.1 g. of aluminum isopropylate in 20 ml. of absolute toluene, and then heated for 45 minutes under gradual distillation. The mixture is then diluted with methylene chloride, washed with 2N sulfuric acid and water, dried, and evaporated. Yield: 11.5 g. of crude 15 α ,16 α -methylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-ol as an oil. A sample purified by preparative layer chromatography and recrystallization from diisopropyl ether/acetone melts at 259°-268° C.

UV: $\epsilon_{241} = 16,500$.

10.5 g. of 15 α ,16 α -methylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'- ξ -ol is combined in 100 ml. of acetone under ice cooling with 10 ml. of chromosulfuric acid (prepared from 267 g. of CrO_3 , 400 ml. of water, and 230 ml. of concentrated sulfuric acid, replenished to a volume of 1 liter with water). The mixture is agitated for 1 hour, then stirred into ice water, washed with water, and taken up in methylene chloride. After drying and evaporation, the residue is chromatographed on silica gel, thus obtaining 8.2 g. of 15 α ,16 α -methylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one. A sample recrystallized from diisopropyl ether/acetone melts at 180°-181° C.

UV: $\epsilon_{240} = 16,600$.

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7.2 g. of 15 α ,16 α -methylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one is combined in 72 ml. of absolute dioxane and 7.2 ml. of triethyl orthoformate with a solution of 7.2 ml. of absolute dioxane and 0.26 ml. of concentrated sulfuric acid. The mixture is stirred for 30 minutes at room temperature. Then, 2 ml. of pyridine is added thereto, the mixture is diluted with ether, washed with water, and dried. After evaporation, 8.5 g. of crude 3-ethoxy-15 α ,16 α -methylene-3,5-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one is obtained.

UV: $\epsilon_{241} = 15,700$.

8.5 g. of 3-ethoxy-15 α ,16 α -methylene-3,5-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one is dissolved in 192 ml. of acetone, cooled in an ice bath, and combined with 1.32 ml. of pyridine, 6.08 g. of sodium acetate, and 60.8 ml. of water; then, 4.51 g. of N-bromosuccinimide is added thereto and within 10 minutes, 6.08 ml. of acetic acid is added dropwise to the reaction mixture. The mixture is further stirred for 1 hour at ice bath temperature, diluted with ether, washed with water, and dried. After evaporation, 9.6 g. of crude 6 β -bromo-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one is obtained.

9.6 g. of 6 β -bromo-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one is stirred in 96 ml. of dimethylformamide with 3.75 g. of lithium carbonate and 4.4 g. of lithium bromide for 18 hours at 100° C. The mixture is then stirred into ice water, the thus-obtained precipitate is filtered off, taken up in methylene chloride, washed with 2N sulfuric acid and water, and dried. After evaporation, the residue is chromatographed on silica gel, thus obtaining 6.5 g. of 15 α ,16 α -methylene-3-oxo-4,6-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one. A sample recrystallized from diisopropyl ether melts at 180.5°-182.5° C.

UV: $\epsilon_{283} = 26,300$.

15 β ,16 β -methylene-3-oxo-4,6-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one

15 g. of 3 β -hydroxy-15 β ,16 β -methylene-5-androstene-17-one (produced, for example, according to German Pat. No. 1,593,500) is reacted in 150 ml. of absolute tetrahydrofuran with 3.27 g. of lithium and 29 ml. of 1-bromo-3-dimethoxypropane for 2 hours at ice bath temperature and for 4 hours at room temperature. The mixture is filtered off from the unreacted lithium, the filtrate is stirred into ice water, the precipitate is filtered off and taken up in methylene chloride. After drying and evaporation, the residue is chromatographed on silica gel. Yield: 17.4 g. of 17 α -(3'-dimethoxypropyl)-15 β ,16 β -methylene-5-androstene-3 β ,17 β -diol.

17.0 g. of 17 α -(3'-dimethoxypropyl)-15 β ,16 β -methylene-5-androstene-3 β ,17 β -diol is agitated in 340 ml. of 70% acetic acid for 18 hours at room temperature. The mixture is then stirred into ice water; the thus-obtained precipitate is filtered off and taken up in methylene chloride. The methylene chloride phase is washed with sodium bicarbonate solution and water, dried, and evaporated, thus obtaining 13.8 g. of 3 β -hydroxy-15 β ,16 β -methylene-5-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-ol as a crude product.

8.8 g. of 3 β -hydroxy-15 β ,16 β -methylene-5-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-ol is combined in 176 ml. of absolute toluene and 17.6 ml. of cyclohexa-

none with 1.76 g. of aluminum isopropylate in 50 ml. of absolute toluene and heated for 3 hours under gradual distillation. The mixture is then diluted with ether, washed with 2N sulfuric acid and water, dried, and evaporated. The residue is chromatographed on silica gel, thus obtaining 4.3 g. of 15 β ,16 β -methylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one. A sample recrystallized from diisopropyl ether/acetone melts at 178.5°-179.5° C.

UV: $\epsilon_{241} = 16,500$.

4.2 g. of 15 β ,16 β -methylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one is refluxed in 84 ml. of tert.-butanol with 4.2 g. of chloranil for 18 hours. The solvent is distilled off under vacuum, and the residue is chromatographed on silica gel. For purposes of additional purification, preparative layer chromatography is employed. Yield: 1.1 g. of 15 β ,16 β -methylene-3-oxo-4,6-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one as an oil.

UV: $\epsilon_{284} = 25,700$.

For each starting material, after the preparative reaction is terminated, the reaction mixture is worked up in a conventional fashion to obtain the desired compound, e.g., by precipitation, extraction, recrystallization, and/or chromatography.

The compounds of this invention possess valuable pharmacological properties. They are, inter alia, diuretics of the aldosterone antagonist type, i.e., they reverse the effect of desoxycorticosterone on the excretion of sodium and potassium. Unexpectedly, the compounds of this invention display superior activity in comparison with the conventional diuretic, spironolactone. This effect can be determined using the test model of Hollman (G. Hollmann et al., "Tubulaere Wirkungen und renale Elimination von Spirolactonen" (Tubular Effects and Renal Elimination of Spirolactones), Naunyn-Schmiedeberg's Arch. Exp. Path. Pharmacol. 247, 419 (1964); P. Marx, "Renal Effects of d-Aldosterone and Its Antagonist Spironolactone," dissertation of the Medical Faculty, Berlin Free University, 1966).

The compounds of Formula I can be administered to mammals, including humans, e.g., parenterally or enterally (orally) in accordance with fully conventional procedures, e.g., those used in the administration of spironolactone. Thus, suitable dosages as a diuretic are 20-500 mg/day for human patients.

The pharmacologically active compounds of Formula I can be processed in accordance with conventional methods of galenic pharmacy to produce medicinal agents, especially for oral administration. Conventional excipients include pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral, enteral or topical application which do not deleteriously react with the active compounds. Suitable pharmaceutically acceptable carriers include, but are not limited to, water, salt solutions, alcohols, vegetable oils, polyethylene glycols, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxy-methylcellulose, polyvinyl pyrrolidone, etc. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influenc-

ing osmotic pressure, buffers, coloring, flavoring and/or aromatic substances and the like which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants, including suppositories. Ampoules are convenient unit dosages.

For enteral application, particularly suitable are tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch. A syrup, elixir or the like can be used wherein a sweetened vehicle is employed. Sustained release compositions can be formulated including those wherein the active compound is protected with differentially degradable coatings, e.g., by microencapsulation, multiple coatings, etc.

Generally, the compounds of this invention are dispensed in unit dosage form comprising 10-100 mg in a pharmaceutically acceptable carrier per unit dosage.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

EXAMPLE 1

1.5 g. of 3-oxo-4,6,15-androstatriene-[17(β -1')-spiro5']perhydrofuran-2'-one is refluxed in 22.5 ml. of methanol with 1.5 ml. of thioacetic acid for 2 hours. The mixture is then diluted with ether, washed with water, sodium bicarbonate solution, and water, dried, and evaporated. The residue is chromatographed on silica gel, thus obtaining 1.05 g. of 7 α -acetylthio-3-oxo-4,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one, m.p. 317°-319° C. (decomposition).

UV: ϵ_{238} = 19,800.

EXAMPLE 2

1.0 g. of 3-oxo-4,6,15-androstatriene-[17(β -1')-spiro-5']perhydrofuran-2'-one is refluxed in 15 ml. of methanol with 1 ml. of thiopropionic acid for 16 hours. The mixture is worked up and purified as described in Example 1, thus obtaining 670 mg. of 3-oxo-7 α -propionylthio-4,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one.

UV: ϵ_{238} = 18,500.

EXAMPLE 3

4.13 g. of trimethyl sulfoxonium iodide is agitated in 75 ml. of dimethyl sulfoxide with 512 mg. of 80% sodium hydride oil suspension for 2 hours under nitrogen. The almost clear solution is combined with 3.0 g. of 3-oxo-4,6,15-androstatriene-[17(β -1')-spiro-5']perhydrofuran-2'-one and agitated for 24 hours at room temperature. The mixture is then stirred into ice water, the precipitate is filtered off, washed with water, and taken up in ether. After drying and evaporation, the residue is chromatographed on silica gel and then further purified by preparative layer chromatography, thus obtaining 520 mg. of 6 β ,7 β -methylene-3-oxo-4,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one.

UV: ϵ_{266} = 18,100.

EXAMPLE 4

1.4 g. of 15 α ,16 α -methylene-3-oxo-4,6-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one is refluxed in 22.5 ml. of methanol with 3 ml. of thioacetic acid for 17 hours. The mixture is then diluted with ether, washed with sodium bicarbonate solution and water, dried, and evaporated. The residue is purified by way of preparative layer chromatography and recrystallized from diisopropyl ether/acetone. Yield: 1.08 g. of 7 α -acetylthio-15 α ,16 α -methylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one, m.p. 214.5°-217.5° C.

UV: ϵ_{238} = 19,100.

EXAMPLE 5

500 mg. of 15 α ,16 α -methylene-3-oxo-4,6-androstadiene-(17(β -1')-spiro-5')perhydrofuran-2'-one is refluxed in 5 ml. of methanol with 1 ml. of thiopropionic acid for 32 hours. The mixture is worked up and purified as described in Example 4. Yield: 220 mg. of 15 α ,16 α -methylene-3-oxo-7 α -propionylthio-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one.

UV: ϵ_{238} = 18,700.

EXAMPLE 6

2.75 g. of trimethyl sulfoxonium iodide is stirred in 57 ml. of dimethyl sulfoxide with 341 mg. of 80% sodium hydride oil suspension for 2 hours at room temperature. The almost clear solution is combined under nitrogen with 2.0 g. of 15 α ,16 α -methylene-3-oxo-4,6-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one and agitated for 24 hours at room temperature. The mixture is then stirred into ice water, the thus-obtained precipitate is filtered off, washed with water, and taken up in methylene chloride. After drying and evaporation, the residue is purified by repeated preparative layer chromatography, thus obtaining 520 mg. of 6 β ,7 β ,15 α ,16 α -dimethylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one.

UV: ϵ_{266} = 18,000.

EXAMPLE 7

1.0 g. of 15 β ,16 β -methylene-3-oxo-4,6-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one is refluxed in 15 ml. of methanol with 1 ml. of thioacetic acid for 2 hours. The mixture is then taken up in ether, washed with sodium bicarbonate solution and water, dried, and evaporated. The residue is chromatographed on silica gel. Recrystallization from diisopropyl ether/acetone yields 590 mg. of 7 α -acetylthio-15 β ,16 β -methylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one, m.p. 242-247° C. (decomposition).

UV: ϵ_{238} = 19,300.

EXAMPLE 8

750 mg. of 15 β ,16 β -methylene-3-oxo-4,6-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one is refluxed in 7.5 ml. of methanol with 0.75 ml. of thiopropionic acid for 18 hours. The mixture is worked up as described in Example 4, and the residue is purified by preparative layer chromatography, thus obtaining 320

mg. of 15 β ,16 β -methylene-3-oxo-7 α -propionylthio-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one as an oil.

UV: $\epsilon_{238} = 18,700$.

EXAMPLE 9

1.4 g. of trimethyl sulfoxonium iodide is stirred in 25 ml. of dimethyl sulfoxide with 170 mg. of 80% sodium hydride oil suspension for 1.5 hours under nitrogen. The almost clear solution is combined with 1.0 g. of 15 β ,16 β -methylene-3-oxo-4,6-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one, dissolved in 10 ml. of dimethyl sulfoxide. After 24 hours of agitation at room temperature, the mixture is stirred into ice water, the precipitate is filtered off, taken up in ether, washed with water, and dried. The residue obtained after evaporation is purified by repeated preparative layer chromatography, thus producing 170 mg. of 6 β ,7 β ,15 β ,16 β -dimethylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one in the form of an oil.

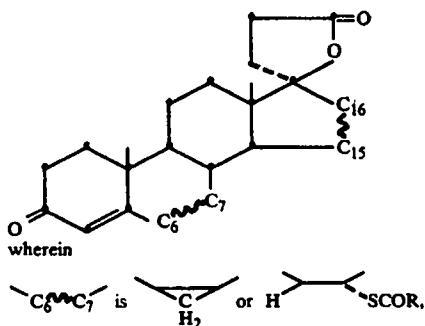
UV: $\epsilon_{266} = 18,400$.

The preceding examples can be repeated with similar success by substituting the generically and specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

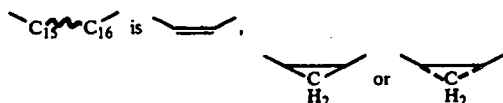
From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

What is claimed is:

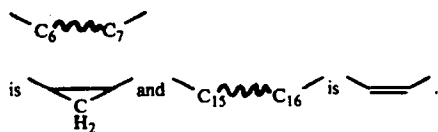
1. A spiro lactone of the formula



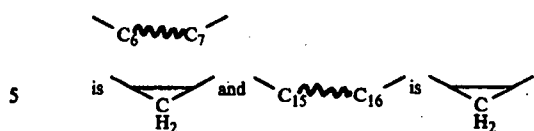
wherein R is lower alkyl of up to 5 carbon atoms, and



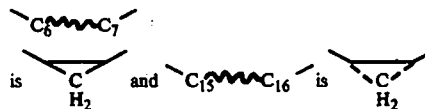
2. The spiro lactone of claim 1 wherein



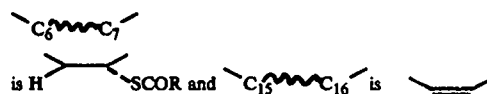
3. The spiro lactone of claim 1 wherein



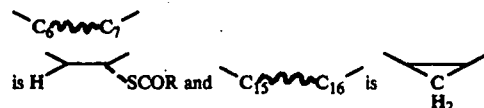
4. The spiro lactone of claim 1 wherein



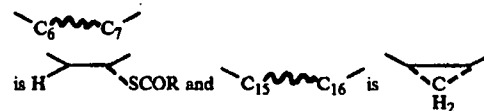
5. The spiro lactone of claim 1 wherein



6. The spiro lactone of claim 1 wherein



7. The spiro lactone of claim 1 wherein



8. The spiro lactone of claim 1 wherein R is methyl or ethyl.

9. 7 α -Acetylthio-3-oxo-4,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one, a compound of claim 1.

10. 3-Oxo-7 α -propionylthio-4,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one, a compound of claim 1.

11. 6 β ,7 β -Methylene-3-oxo-4,15-androstadiene-[17(β -1')-spiro-5']perhydrofuran-2'-one, a compound of claim 1.

12. 15 α ,16 α -Methylene-3-oxo-7 α -propionylthio-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one, a compound of claim 1.

13. 6 β ,7 β ,15 α ,16 α -Dimethylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one, a compound of claim 1.

14. 7 α -Acetylthio-15 α ,16 α -methylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one, a compound of claim 1.

15. 7 α -Acetylthio-15 β ,16 β -methylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one, a compound of claim 1.

16. 15 β ,16 β -Methylene-3-oxo-7 β -propionylthio-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one, a compound of claim 1.

17. 6 β ,7 β ,15 β ,16 β -Dimethylene-3-oxo-4-androstene-[17(β -1')-spiro-5']perhydrofuran-2'-one, a compound of claim 1.

18. A pharmaceutical composition which comprises a diuretically effective amount of a spiro lactone of claim 1 and a pharmaceutically acceptable adjuvant.

19. The method of achieving diuretic effects in mammals which comprises administering a diuretically effective amount of a spiro lactone of claim 1.

* * * * *

ANEXO 2

12

EUROPEAN PATENT APPLICATION

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54 **Combination dosage form for premenopausal women.**

57 Disclosed herein is a method of providing hormonal replacement therapy and contraception for a pre-menopausal woman, which comprises administering to a pre-menopausal woman in need thereof a combination dosage form of an estrogen selected from

0.5-2.0 mg. of 17 β -estradiol,
0.008-0.030 mg. of ethinyl estradiol, and
0.015-0.060 mg. of mestranol;
and a progestogen selected from
0.025-0.100 mg. of levonorgestrel,
0.010-0.070 mg. of gestodene,
0.025-0.100 mg. of desogestrel,
0.025-0.100 mg. of 3-ketodesogestrel, and
0.085-0.35 mg. of norethindrone,

said combination dosage form being administered for 23-25 days beginning at day one of the menstrual cycle, followed by 2-5 pill-free or blank pill days, for a total of 28 days in the administration cycle. The preferred dosage form of the invention is a combination of 1 mg. of 17 β -estradiol and 0.050 or 0.075 mg. of levonorgestrel. The preferred administration cycle of the invention is administration of the combination dosage form for the first 24 days of the menstrual cycle and no dosage form for the last 4 days of the menstrual cycle.

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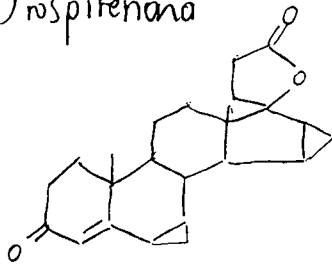
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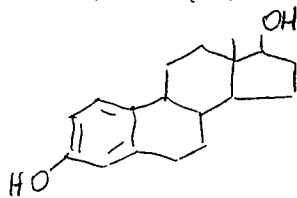
Asociación Estrógeno-Progestágeno

ESTROGEN

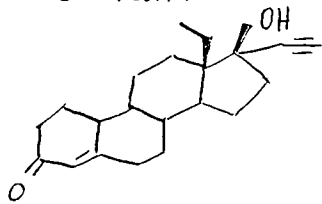
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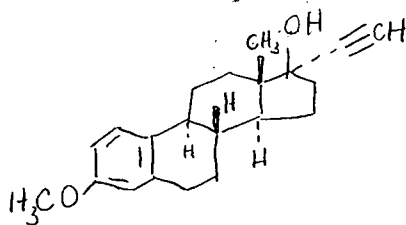
17. β -estradiol



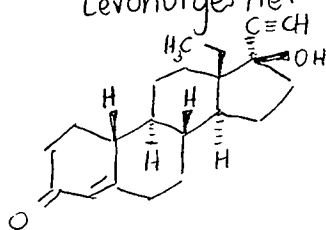
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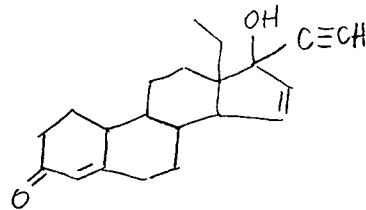


Levonorgestrel

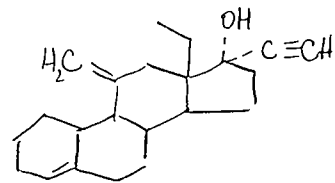


PROGESTOGEN.

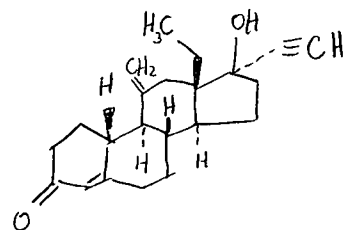
Gestodene



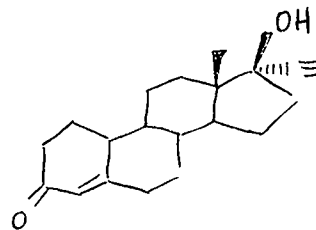
Desogestrel



3-keto desogestrel



Norethindrone



COMBINATION DOSAGE FORM FOR PRE-MENOPAUSAL WOMEN

The subject invention provides hormonal replacement therapy and contraceptive protection for the pre-menopausal woman in need thereof. Such therapy and contraceptive protection is provided by a combination dosage form of the invention which comprises a low dose of an estrogen combined with a very low dose of a progestogen. A preferred combination dosage form of the invention comprises 0.5-2.0 mg. of 17β -estradiol and 0.025-0.100 mg. of levonorgestrel. The combination dosage form of the invention is administered for the first 23-26 days of the menstrual cycle, followed by 2-5 pill-free or blank pill days, for a total of 28 days in the administration cycle. The preferred administration cycle is 24 days of the combination dosage form and 4 days of no dosage form.

Pre-menopause is defined as the time around 40 years of age when a woman can reasonably be said to be approaching menopause (the last menstrual period) or the time when a woman feels the approach of menopause by experiencing pre-menopausal irregularities in her menstrual cycle or other hypoestrogenic symptoms.

The woman over forty is in a transitional period in which her hormone levels are waning; she still ovulates and yet she experiences many of the symptoms of the hypoestrogenic woman, insomnia, hot flushes, irritability, etc. The fact that these women are still menstruating has led to the uniformed attitude that her complaints are psychosomatic in origin.

The climacteric is marked by many changes due to the natural aging process; all of which are modified by individual life-styles. Both natural and surgical menopause appear to be associated with adverse changes in metabolic parameters and in hormone levels. For example, the metabolic change in the blood lipid profile of the post-menopausal woman may lead to the development of atherosclerosis, hypertension and coronary heart disease. See Notelovitz M, Graig SK, Rappaport V, et al; "Menopausal status associated with increased inhibition of blood coagulation," *Am J Obstet Gynecol* 141:149, (1981); Notelovitz M, Greig HBW, "Natural estrogen and anti-thrombin III activity in postmenopausal women," *J Reprod Med* 16:87 (1976); Nielsen FH, Honore E, Kristoffersen K, et al, "Changes in serum lipids during treatment with norgestrel, estradiol-valerate and cycloprogyron." *Acta Obstet Gynecol Scand* 56:367 (1977) and Paterson MEL, Sturdee DW, Moore B, "The effect of various regimens of hormone therapy on serum cholesterol and triglyceride concentrations in postmenopausal women," *Br J Obstet Gynecol* 87:552 (1980). Ad-

verse changes in hormonal levels of the post-menopausal woman are associated with endometrial and breast cancer and with osteoporosis. See Gambrell RD Jr, Bagnell CA, Greenblatt RB, "Role of estrogens and progesterone in the etiology and prevention of endometrial cancer: Review," *Am J Obstet Gynecol* 146:696 (1983); Gambrell RD Jr, "The prevention of endometrial cancer in postmenopausal women with progestogen," *Maturitas* 1:107 (1978); and Nachtigall LE, Nachtigall RH, Nachtigall RD, et al, "Estrogen replacement therapy: I. A 10-year prospective study in the relationship to osteoporosis," *Obstet Gynecol* 53:277, (1979).

The years after 40 witness an ever increasing number of anovulatory cycles, leaving a woman still menstruating but exposed to variable periods of unopposed estrogen. It is impossible to predict which cycles will be ovulatory or anovulatory because of the absence of any consistent pattern. Thus, the pre-menopausal woman also needs constant contraceptive protection. If one considers the mortality rate in the aging woman due to late childbirth, this contraceptive need becomes of paramount importance. Therefore, in consideration of the appropriate hormone therapy for the pre-menopausal woman, attention must be focused on the effects of such therapy on metabolic parameters as well as on reproductive target organs. In the pre-menopausal woman it is necessary that such therapy also be contraceptive.

In a first aspect, this invention provides a method of providing hormonal replacement therapy and contraception for a pre-menopausal woman, which comprises administering to a pre-menopausal woman in need thereof a combination dosage form of an estrogen selected from

0.5-2.0 mg. of 17β -estradiol,
0.008-0.030 mg. of ethinyl estradiol, and
0.015-0.060 mg. of mestranol;

and a progestogen selected from
0.025-0.100 mg. of levonorgestrel,
0.010-0.70 mg. of gestodene,
0.025-0.100 mg. of desogestrel,
0.025-0.100 mg. of 3-ketodesogestrel, and
0.085-0.35 mg. of norethindrone,

said combination dosage form being administered for 23-26 days beginning at day one of the menstrual cycle, followed by 2-5 pill-free or blank pill days, for a total of 28 days in the administration cycle.

In a second aspect, this invention provides a combination dosage form for hormonal replacement therapy and contraception for a pre-menopausal woman, comprising a combination of an

estrogen selected from
 0.5-2.0 mg. of 17β -estradiol
 0.008-0.030 mg. of ethinyl estradiol, and
 0.015-0.060 mg. of mestranol;
 and a progestogen selected from
 0.025-0.100 mg. of levonorgestrel,
 0.010-0.070 mg. of gestodene,
 0.025-0.100 mg. of desogestrel, and
 0.025-0.100 mg. of 3-ketodesogestrel, and
 0.085-0.35 mg. of norethindrone,
 said combination dosage form being administered
 for 23 - 26 days beginning at day one of the
 menstrual cycle, followed by 2-5 pill-free or blank
 pill days, for a total of 28 days in the administration
 cycle.

In the third aspect the invention provides the
 use of a composition comprising an estrogen se-
 lected from

0.5-2.0 mg. of 17β -estradiol
 0.008-0.030 mg. of ethinyl estradiol, and
 0.015-0.060 mg. of mestranol;
 and a progestogen selected from
 0.025-0.100 mg. of levonorgestrel,
 0.010-0.070 mg. of gestodene,
 0.025-0.100 mg. of desogestrel,
 0.025-0.100 mg. of 3-ketodesogestrel, and
 0.085-0.35 mg. of norethindrone,

for the manufacture of a dosage form for providing
 hormonal replacement therapy and contraception
 for a pre-menopausal woman by administration of
 the dosage form for 23 to 26 days beginning at day
 one of the menstrual cycle, followed by 2 to 5 pill-
 free or blank pill days, for a total of 28 days in the
 administration cycle.

A fourth aspect of the invention provides a
 pack for providing hormonal replacement therapy
 and contraception for a pre-menopausal woman
 which pack comprises 23-26 dosage forms each
 comprising an estrogen selected from

(a) 0.5-2.0 mg. of 17β -estradiol
 0.008-0.030 mg. of ethinyl estradiol, and
 0.015-0.060 mg. of mestranol;
 and a progestogen selected from
 0.025-0.100 mg. of levonorgestrel,
 0.010-0.70 mg. of gestodene,
 0.025-0.100 mg. of desogestrel,
 0.025-0.100 mg. of 3-ketodesogestrel, and
 0.085-0.35 mg. of norethindrone

(b) 2 to 5 blank pills or other indications to
 indicate that the daily administration of the 23 to 26
 dosage forms should be followed by 2 to 5 pill free
 or blank pill days.

For all aspects of the invention the preferred
 estrogen is 17β -estradiol and the preferred pro-
 gestogen is levonorgestrel. For all aspects of the
 invention a preferred dosage range of the estrogen
 component is:

0.75-1.50 mg. of 17β -estradiol,

0.012-0.025 mg. of ethinyl estradiol, and
 0.025-0.050 mg. of mestranol; and
 a preferred dosage range of the progestogen com-
 ponent is:

5 0.035-0.085 mg. of levonorgestrel,
 0.015-0.060 mg. of gestodene,
 0.035-0.085 mg. of desogestrel,
 0.035-0.085 mg. of 3-ketodesogestrel, and
 0.010-0.30 mg. of norethindrone.

10 For all aspects of the invention the preferred es-
 trogens are 17β -estradiol, ethinyl estradiol and
 mestranol; and the preferred progestogens are
 levonorgestrel, gestodene, desogestrel and 3-
 ketodesogestrel. 17β -estradiol and levonorgestrel
 15 are particularly preferred. Gestodene is also a par-
 ticularly preferred progestogen. A particularly pre-
 ferred combination dosage form for all aspects of
 the invention is a combination in which the es-
 trogen is in a dose of 1 mg. of 17β -estradiol or an
 20 equivalent dose of ethinyl estradiol or mestranol
 and the progestogen is in a dose of 0.050 mg. of
 levonorgestrel or an equivalent dose of gestodene,
 desogestrel or 3-ketodesogestrel. A further particu-
 25 larly preferred combination dosage form for both
 aspects of the invention is a combination in which
 the estrogen is in a dose of 1 mg. of 17β -estradiol
 or an equivalent dose of ethinyl estradiol or
 mestranol and the progestogen is in a dose of
 30 0.075 mg. of levonorgestrel or an equivalent dose
 of gestodene, desogestrel, or 3-ketodesogestrel. A
 preferred course of administration for all aspects of
 the invention is administration of the combination
 dosage form of the invention for the first 24 days of
 the menstrual cycle and no dosage form (i.e. pill-
 35 free) or a blank dosage form for the last 4 days of
 the menstrual cycle. A further preferred course of
 administration for all aspects of the invention is
 administration of the combination dosage form for
 the first 23 days of the menstrual cycle and no
 40 dosage form (i.e. pill-free) or a blank dosage form
 for the last 5 days of the menstrual cycle. The
 preferred doses equivalent to 1 mg. of 17β -es-
 tradiol are, approximately: ethinyl estradiol 0.015
 mg. and mestranol 0.030 mg. The preferred doses
 45 equivalent to 0.050 mg. of levonorgestrel are ap-
 proximately: gestodene 0.035 mg., desogestrel and
 3-ketodesogestrel 0.050 mg., and norethindrone
 0.175 mg. The preferred doses equivalent to 0.075
 mg. of levonorgestrel are, approximately:
 50 gestodene 0.052 mg., desogestrel and 3-
 ketodesogestrel 0.075 mg., and norethindrone 0.25
 mg. Such equivalent doses may vary depending
 upon the physiological effect desired and the assay
 method used.

55 An especially preferred method of the invention
 comprises administering to a pre-menopausal
 woman in need thereof a combination dosage form
 of 1 mg. of 17β -estradiol and 0.050 mg. of levonor-

gestrel or 1 mg. of 17β -estradiol and 0.075 mg. of levonorgestrel for 23-26 days beginning at day one of the menstrual cycle, followed by 2-5 pill-free or blank-pill days, for a total of 28 days in the administration cycle. An especially preferred combination dosage form of the invention for providing hormonal replacement therapy and contraception for a pre-menopausal woman comprises a combination dosage form of 1 mg. of 17β -estradiol and 0.050 mg. of levonorgestrel or 1 mg. of 17β -estradiol and 0.075 mg. of levonorgestrel, said combination dosage form being administered for 23-26 days beginning at day one of the menstrual cycle, followed by 2-5 pill-free or blank-pill days, for a total of 28 days in the administration cycle. For all aspects of the invention, the preferred cycle of administration is administration of the combination dosage form for the first 24 days of the menstrual cycle and administration of no dosage form or a blank dosage form for the last 4 days of the menstrual cycle. Or, administration of the combination dosage form for the first 23 days of the menstrual cycle and no dosage form or a blank dosage form for the last 5 days is also preferred. A preferred dose of ethinyl estradiol equivalent to the preferred dose of 1 mg. of 17β -estradiol is 0.015 mg. The equivalent preferred dose of mestranol is 0.030 mg. The preferred equivalent doses of desogestrel and 3-ketodesogestrel which are equivalent to the preferred doses of levonorgestrel, namely, 0.050 mg. and 0.075 mg. are also 0.050 mg. and 0.075 mg. The equivalent preferred doses of gestodene to 0.050 mg. and 0.075 mg. of levonorgestrel are 0.035 mg. and 0.052 mg.

It is to be understood that in this specification and the accompanying claims norgestrel may be used in place of levonorgestrel, but at twice the stated dose of levonorgestrel. The accompanying claims should be construed accordingly. Norgestrel is a racemic compound while levonorgestrel is one of the optically active isomers. Levonorgestrel is particularly preferred.

The progestogen levonorgestrel is well known and has been marketed in oral contraceptive formulations (at doses of 0.15 mg. and higher) for many years. Its chemical name is (-)-13-ethyl-17-hydroxy-18,19-dinorepregn-4-en-20-yn-3-one. Norgestrel's common name is 17α -ethynyl-18-homo-18-nortestosterone. Gestodene, deogestrel, and 3-ketodesogestrel are newer progestogens in various stages of clinical development and use. The new compound, gestodene, differs from norgestrel by a double bond in the 15 position and is progestationally active per se, whereas desogestrel is believed to be inactive as the parent molecule and is thought to undergo two metabolic steps for progestational activity. Desogestrel is believed to be metabolized first to the biologically active 3β -

hydroxydesogestrel with estrogenic/androgenic activity and then to 3-ketodesogestrel, which has progestogenic activity; it differs from norgestrel by a methylene group at position 11. Norethindrone's chemical name is 17-hydroxy-19-norepregn-4-en-20-yn-3-one. It is also known as 19-norethisterone or norethisterone. Norethindrone acetate may be used in place of norethindrone, and hence the term "norethindrone" in the accompanying claims is to be understood as referring to either the free alcohol or its acetate.

17β -estradiol is the most potent naturally occurring estrogen in mammals. Its chemical name is estra-1,3,5(10)-triene-3,17-diol. 17β -estradiol (or β -estradiol) is its common name. Ethinyl estradiol and mestranol are both synthetic estrogens which have an ethinyl group at the 17 position of the estradiol ring structure. Mestranol additionally has a methoxy group rather than a hydroxy group at the 3 position of the estradiol ring structure. Ethinyl estradiol and mestranol are used in oral contraceptive-formulations. The composition of such marketed oral contraceptives is shown in Table 15-2 on page 454 in Chapter 15 "Fertility Control and its Complications" by Bruce R. Carr and James E. Griffin in Williams Textbook of Endocrinology, seventh edition, (Jean D. Wilson M.D. and Daniel W. Foster M.D. (W.B. Saunders Company, Philadelphia, 1985).

An example of a pack which may be used in the fourth aspect of the invention or for providing the dosage forms for use by the patient in other aspects of the invention is a blister pack type product as is commonly used with oral contraceptive products. Such product would normally comprise the appropriate number of dosage tablets in a sealed blister pack in a cardboard, paperboard or plastic sleeve with a protective cover or box. Each combination dosage tablet blister container may be numbered or otherwise marked for the first 23-26 days of the menstrual cycle, [as, for example, prescribed by the patient's physician]. The remaining 2-5 (pill-free) days of the 28 day administration cycle would contain blank-pills or unfilled blisters or other marking devices to assist the patient in following the prescribed administration cycle. The combination estrogen and progestogen dosage form of the invention is preferably provided as a tablet, caplet or capsule in a manner known in the art. Similarly a blank pill is preferably a tablet, caplet or capsule containing no active hormonal agents. Other oral or parenteral dosage preparations or packages may be provided as known in the art.

Claims

1. The use of a composition comprising an estrogen selected from

0.5-2.0 mg. of 17β -estradiol
0.008-0.030 mg. of ethinyl estradiol, and
0.015-0.080 mg. of mestranol;

and a progestogen selected from

0.025-0.100 mg. of levonorgestrel,
0.010-0.070 mg. of gestodene,
0.025-0.100 mg. of desogestrel,
0.025-0.100 mg. of 3-ketodesogestrel, and
0.085-0.35 mg. of norethindrone,

for the manufacture of a dosage form for providing hormonal replacement therapy and contraception for a pre-menopausal woman by administration of the dosage form for 23 to 26 days beginning at day one of the menstrual cycle, followed by 2 to 5 pill-free or blank pill days, for a total of 28 days in the administration cycle.

2. The use as claimed in Claim 1 in which the estrogen is 17β -estradiol.

3. The use as claimed in Claim 1 or 2 in which the progestogen is levonorgestrel.

4. The use as claimed in Claim 1 or 2 in which the progestogen is gestodene, desogestrel or 3-ketodesogestrel.

5. The use as claimed in Claim 1 in which the dosage form comprises an estrogen selected from:

0.75-1.50 mg. of 17β -estradiol,
0.012-0.025 mg. of ethinyl estradiol, and
0.025-0.050 mg. of mestranol; and

a progestogen selected from:

0.035-0.085 mg. of levonorgestrel,
0.015-0.060 mg. of gestodene,
0.035-0.085 mg. of desogestrel,
0.035-0.085 mg. of 3-ketodesogestrel, and
0.10-0.30 mg. of norethindrone.

6. The use as claimed in Claim 1 in which the estrogen is in a dose of 1 mg. of 17β -estradiol or an equivalent dose of ethinyl estradiol or mestranol and the progestogen is in a dose of 0.050 mg. of levonorgestrel or an equivalent dose of gestodene, desogestrel or 3-ketodesogestrel.

7. The use as claimed in Claim 1 in which the estrogen is in a dose of 1 mg. of 17β -estradiol or an equivalent dose of ethinyl estradiol or mestranol and the progestogen is in a dose of 0.075 mg. or levonorgestrel or an equivalent dose of gestodene, desogestrel or 3-ketodesogestrel.

8. A pack for providing a hormonal replacement therapy and contraception for a pre-menopausal woman which pack comprises

(a) 23 to 26 dosage forms each comprising an estrogen selected from:

0.5-2.0 mg. of 17β -estradiol
0.008-0.030 mg. of ethinyl estradiol, and
0.015-0.060 mg. of mestranol;

and a progestogen selected from

0.025-0.100 mg. of levonorgestrel,
0.010-0.070 mg. of gestodene,
0.025-0.100 mg. of desogestrel
0.025-0.100 mg. of 3-ketodesogestrel, and
0.085-0.35 mg. of norethindrone

and

(b) 2 to 5 blank pills or other indications to indicate that the daily administration of the 23 to 26 dosage forms should be followed by 2 to 5 pill free or blank pill days.

9. A pack as claimed in Claim 8 in which the estrogen selected is 17β -estradiol.

10. A pack as claimed in Claim 8 or 9 in which the progestogen selected is levonorgestrel.

11. A pack as claimed in Claim 8 in which the estrogen is selected from:

0.75-1.50 mg. of 17β -estradiol,
0.012-0.025 mg. of ethinyl estradiol, and
0.025-0.050 mg. of mestranol; and

the progestogen is selected from:

0.035-0.085 mg. of levonorgestrel,
0.015-0.060 mg. of gestodene,
0.035-0.085 mg. of desogestrel,
0.035-0.085 mg. of 3-ketodesogestrel, and
0.10-0.30 mg. of norethindrone.

12. A pack as claimed in Claim 8 in which the estrogen is in a dose of 1 mg. of 17β -estradiol or an equivalent dose of ethinyl estradiol or mestranol and the progestogen is in a dose of 0.050 mg. of levonorgestrel or an equivalent dose of gestodene, desogestrel or 3-ketodesogestrel.

13. A pack as claimed in Claim 8 in which the estrogen is in a dose of 1 mg. of 17β -estradiol or an equivalent dose of ethinyl estradiol or mestranol and the progestogen is in a dose of 0.075 mg. of levonorgestrel or an equivalent dose of gestodene, desogestrel or 3-ketodesogestrel.

14. A pack as claimed in any one of Claims 8 to 13 which comprises 24 dosage forms and 4 blank pills or other indications to indicate that no dosage form or a blank pill is administered for the last 4 days of the menstrual cycle.

15. A pack as claimed in any one of Claims 8 to 13 which comprises 23 dosage forms and 5 blank pills or other indications to indicate that no dosage form or a blank pill is administered for the last 5 days of the menstrual cycle.

16. A pack according to Claim 8 comprising 24 dosage forms each comprising 1 mg. of 17β -estradiol and 0.50 mg. or 0.075 mg. levonorgestrel and 4 blank pills or other indications to indicate that no dosage form or a blank pill is administered for the last 4 days of the menstrual cycle.

17. A pack according to Claim 8 comprising 23 dosage forms each comprising 1 mg. of 17β -estradiol and 0.50 mg. or 0.075 mg. of levonorgestrel

and 5 blank pills or other indications to indicate that no dosage form or a blank pill is administered for the last 5 days of the menstrual cycle.

Claims for the following Contracting States: ES, GR, AT

1. The use of a composition comprising an estrogen selected from

0.5-2.0 mg. of 17β -estradiol
0.008-0.030 mg. of ethinyl estradiol, and
0.015-0.060 mg. of mestranol;

and a progestogen selected from

0.025-0.100 mg. of levonorgestrel,
0.010-0.070 mg. of gestodene,
0.025-0.100 mg. of desogestrel,
0.025-0.100 mg. of 3-ketodesogestrel, and
0.085-0.35 mg. of norethindrone,

for the manufacture of a dosage form for providing hormonal replacement therapy and contraception for a pre-menopausal woman by administration of the dosage form for 23 to 26 days beginning at day one of the menstrual cycle, followed by 2 to 5 pill-free or blank pill days, for a total of 28 days in the administration cycle.

2. The use as claimed in Claim 1 in which the estrogen is 17β -estradiol.

3. The use as claimed in Claim 1 or 2 in which the progestogen is levonorgestrel.

4. The use as claimed in Claim 1 or 2 in which the progestogen is gestodene, desogestrel or 3-ketodesogestrel.

5. The use as claimed in Claim 1 in which the dosage form comprises an estrogen selected from:

0.75-1.50 mg. of 17β -estradiol,
0.012-0.025 mg. of ethinyl estradiol, and
0.025-0.050 mg. of mestranol; and

a progestogen selected from:

0.035-0.085 mg. of levonorgestrel,
0.015-0.060 mg. of gestodene,
0.035-0.085 mg. of desogestrel,
0.035-0.085 mg. of 3-ketodesogestrel, and
0.10-0.30 mg. of norethindrone.

6. The use as claimed in Claim 1 in which the estrogen is in a dose of 1 mg. of 17β -estradiol or an equivalent dose of ethinyl estradiol or mestranol and the progestogen is in a dose of 0.050 mg. of levonorgestrel or an equivalent dose of gestodene, desogestrel or 3-ketodesogestrel.

7. The use as claimed in Claim 1 in which the estrogen is in a dose of 1 mg. of 17β -estradiol or an equivalent dose of ethinyl estradiol or mestranol and the progestogen is in a dose of 0.075 mg. or levonorgestrel or an equivalent dose of gestodene, desogestrel or 3-ketodesogestrel.

8. A process for preparing a pack for providing a hormonal replacement therapy and contraception for a premenopausal woman which process comprises associating

(a) 23 to 26 dosage forms each comprising an estrogen selected from:

0.5-2.0 mg. of 17β -estradiol
0.008-0.030 mg. of ethinyl estradiol, and
0.015-0.060 mg. of mestranol;

and a progestogen selected from

0.025-0.100 mg. of levonorgestrel,
0.010-0.070 mg. of gestodene,
0.025-0.100 mg. of desogestrel
0.025-0.100 mg. of 3-ketodesogestrel, and
0.085-0.35 mg. of norethindrone

with

(b) 2 to 5 blank pills or other indications to indicate that the daily administration of the 23 to 26 dosage forms should be followed by 2 to 5 pill free or blank pill days.

9. A process as claimed in Claim 8 in which the estrogen selected is 17β -estradiol.

10. A process as claimed in Claim 8 or 9 in which the progestogen selected is levonorgestrel.

11. A process as claimed in Claim 8 in which the estrogen is selected from:

0.75-1.50 mg. of 17β -estradiol,
0.012-0.025 mg. of ethinyl estradiol, and
0.025-0.050 mg. of mestranol; and

the progestogen is selected from:

0.035-0.085 mg. of levonorgestrel,
0.015-0.060 mg. of gestodene,
0.035-0.085 mg. of desogestrel,
0.035-0.085 mg. of 3-ketodesogestrel, and
0.10-0.30 mg. of norethindrone.

12. A process as claimed in Claim 8 in which the estrogen is in a dose of 1 mg. of 17β -estradiol or an equivalent dose of ethinyl estradiol or mestranol and the progestogen is in a dose of 0.050 mg. of levonorgestrel or an equivalent dose of gestodene, desogestrel or 3-ketodesogestrel.

13. A process as claimed in Claim 8 in which the estrogen is in a dose of 1 mg. of 17β -estradiol or an equivalent dose of ethinyl estradiol or mestranol and the progestogen is in a dose of 0.075 mg. of levonorgestrel or an equivalent dose of gestodene, desogestrel or 3-ketodesogestrel.

14. A process as claimed in any one of Claims 8 to 13 which comprises 24 dosage forms and 4 blank pills or other indications to indicate that no dosage form or a blank pill is administered for the last 4 days of the menstrual cycle.

15. A process as claimed in any one of Claims 8 to 13 which comprises 23 dosage forms and 5 blank pills or other indications to indicate that no dosage form or a blank pill is administered for the last 5 days of the menstrual cycle.

16. A process according to Claim 8 comprising 24 dosage forms each comprising 1 mg. of 17 β -estradiol and 0.50 mg. or 0.075 mg. levonorgestrel and 4 blank pills or other indications to indicate that no dosage form or a blank pill is administered for the last 4 days of the menstrual cycle. 5

17. A process according to Claim 8 comprising 23 dosage forms each comprising 1 mg. of 17 β -estradiol and 0.50 mg. or 0.075 mg. of levonorgestrel and 5 blank pills or other indications to indicate that no dosage form or a blank pill is administered for the last 5 days of the menstrual cycle. 10

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US005569652A

United States Patent [19]

Beier et al.

[11] **Patent Number:** 5,569,652[45] **Date of Patent:** Oct. 29, 1996[54] **DIHYDROSPIRORENONE AS AN ANTIANDROGEN**[75] **Inventors:** Sybille Beier; Walter Elger; Yukishige Nishino; Rudolf Wiechert, all of Berlin, Germany[73] **Assignee:** Schering Aktiengesellschaft, Berlin, Germany[21] **Appl. No.:** 162,387[22] **Filed:** Dec. 7, 1993**Related U.S. Application Data**

[63] Continuation of Ser. No. 835,000, Feb. 14, 1992, abandoned, which is a continuation of Ser. No. 524,396, May 16, 1990.

[30] **Foreign Application Priority Data**

May 16, 1989 [DE] Germany 39 16 112.9

[51] **Int. Cl.⁶** **A61K 31/585**[52] **U.S. Cl.** **514/173; 514/172**[58] **Field of Search** 514/173, 172; 540/11, 8[56] **References Cited****U.S. PATENT DOCUMENTS**

4,347,245	8/1982	Shapiro	424/241
4,502,989	3/1985	Kamata et al.	552/615
4,584,288	4/1986	Nickish et al.	514/172
4,729,999	3/1988	Young	514/227
4,855,289	8/1989	Wester et al.	514/171
4,868,166	9/1989	Bittler et al.	514/173

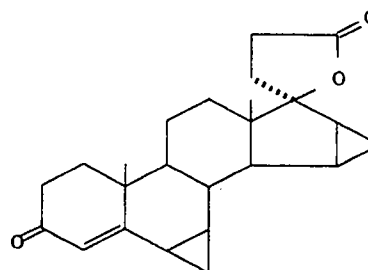
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OTHER PUBLICATIONSBreiner et al., "Inhibition of Androgen Receptor Binding by Natural and Synthetic Steroids in Cultured Human Genital Skin Fibroblasts," *Klin. Wochenschr.*, 64:732-737 (1986).Nishino et al., *Arch Pharmacol.*, vol. 316, R49 (1981).Nishino et al., *Acta Endocrinologica, Suppl.* 246, vol. 99, p. 93, Abstract 105 (1982).*Primary Examiner*—Theodore J. Criares*Attorney, Agent, or Firm*—Millen, White, Zelano, & Branigan, P.C.[57] **ABSTRACT**

Dihydrospirorenone,



preferably together with an estrogen, can be used for the production of a pharmaceutical agent suitable for treatment of hormonal irregularities during premenopause (menstruation stabilization), for hormonal substitution therapy during menopause, for treatment of androgen-induced disorders and/or for contraception.

27 Claims, No Drawings

Nivel Inventivo

Dihidrospirorenono +
Estrógeno (etinil-estradiol)

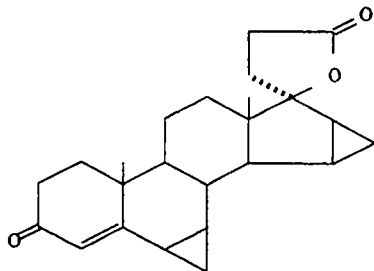
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DIHYDROSPIRORENONE AS AN ANTIANDROGEN

This application is a continuation of application Ser. No. 07/835,000, filed Feb. 14, 1992, ABN, which is a continuation of Ser. No. 07/524,396, filed May 16, 1990.

BACKGROUND OF THE INVENTION

This invention relates to the use of the compound of formula I



for the production of a pharmaceutical agent.

Compound I (dihydrospirorenone) is described in DE A-26 52 761, among others, as a diuretic of the aldosterone-antagonist type.

It can be seen from DE-A 30 22 337 that compound I, at doses at which the antialdosterone effect already appears, also exhibits a marked gestagen effect. Therefore, compound I can be used alone or in combination with estrogens in contraceptive preparations.

According to DE-A 30 22 337, these preparations are to be used for women who desire contraception and suffer from high blood pressure or in whom blood pressure rises when they take oral contraceptives. Thus, also for women predisposed to increased blood pressure, hormonal contraception is possible.

A combined preparation for substitution therapy and contraception for women before menopause (starting at about age 40) is known from EP-A 0253 607. This combined preparation contains an estrogen from the group

17beta-estradiol,
ethynylestradiol and
mestranol
and a gestagen from the group
levonorgestrel,
gestodene,
desogestrel,
3 ketodesogestrel and
norethindrone.

A composition so selected should balance hormonal irregularities in the transition phase of premenopause and help to alleviate the discomfort caused by the hormonal change of the female organism during this phase. Simultaneously, such a composition guarantees the contraceptive protection still necessary at this age.

For various, known reasons and because of the increase in the incidence of contraindications with increasing age, the taking of the usual hormonal contraceptives is recommended for women only until about age 35, so that a hormonal treatment during premenopause and a substitution therapy during menopause using doses that simultaneously have a contraceptive effect can be considered problematic.

Besides these circumstances justifying contraindication, in women of such advanced age, symptoms of androgeni-

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zation such as, for example, beard growth, deepening of the voice and impure skin are often observed; further, a rise in blood pressure can often be noted.

Thus, there remains a need for good agents for hormonal therapy, especially for such woman, including achievement of one or more of such effects.

SUMMARY OF THE INVENTION

It has now been found that the compound of formula I, in addition to its gestagen and antialdosterone effect, surprisingly exhibits a strong antiandrogenic activity component, and specifically at doses that also make possible the formulation of this compound as an oral contraceptive. Dihydrospirorenone acts as an antiandrogen about as strongly as cyproterone acetate, considered the standard compound (same maximum effect). (Animal model: juvenile, castrated and testosterone-substituted male rat.)

This invention thus relates to the use of the compound of formula I for the production of a pharmaceutical agent suitable for treatment of hormonal irregularities during premenopause (e.g., menstruation stabilization) and/or for hormonal substitution therapy during menopause and/or for treatment of androgen-induced disorders and/or for contraception. Conventional protocols can be used to determine antiandrogenic activity, e.g., as disclosed in *Methods in Hormone Research*, Editor: R. I. Dorfman, Academic Press, New York, London, 1969, pp. 241; or *Androgens and Antiandrogens*, Editors: L. Martin and M. Motta, Raven Press, New York, 1977, pp. 163.

Thus, in various aspects, this invention relates to a method of achieving an antiandrogenic effect comprising administering I to a patient in need of antiandrogenic treatment; to a method of treating an androgen induced disorder in a female comprising administering I; to a method of achieving a contraceptive effect in a female during premenopause or menopause (both terms having their conventional meaning, e.g., as shown in "The Controversial Climacteric," P. A. van Keep et al., Ed., MTP Press (1981), e.g., page 9) comprising administering to the female an effective amount of I; to a method of treating gestagen-related hormonal irregularities in a female during premenopause comprising administering I; and/or to a method of achieving gestogen-related hormonal substitution therapy in a female in menopause comprising administering I. In preferred aspects, the females are suffering from and/or predisposed to high blood pressure disorders and/or to androgen-related disorders.

Preferably an estrogen is used together with the compound of formula I. Whether a synthetic or a natural estrogen is preferably used depends on whether the contraceptive effect or the substitutive effect is emphasized: in the first case, ethynylestradiol or another synthetic estrogen is preferred, in the second case, such a pharmaceutical agent should contain a natural estrogen.

But in any case, such a pharmaceutical agent guarantees a woman of middle age (about age 35-55) a stabilization of her menstruation cycle and the contraception still indispensable at this age, with simultaneous, favorable influence on androgen-induced disorders. Of course, this pharmaceutical agent is also suited for younger women, especially for those that have a particular predisposition toward high blood pressure and/or suffer from symptoms of androgenization or are predisposed to one or both of these, e.g., in view of their past medical history, family background, etc., in addition to age.

Here such a use is especially effective because the compound of formula I simultaneously combines a gestagen,

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antialdosterone effect as well as a strong antiandrogen effect. Previously no substance was known that simultaneously exhibited these three properties.

The dose of the compound of formula I can be 0.5 to 50 mg per day, preferably 1-10 mg per day for all uses of this invention.

Suitable as estrogens are all previously known estrogens. The estrogen used preferably for the various purposes of this invention should be administered in doses such that the estrogen amount used according to the invention is equal to that which corresponds to the administration of 0.02 to 0.04 mg of 17alpha-ethynylestradiol or 0.5 to 4.0 mg of estradiol valerate daily. Such amounts can be conventionally determined using fully conventional tests such as described in Dorfman, *supra*, page 62. As estrogenic components, among others the 17alpha-ethynyl-estradiol esters and ethers are suitable as well as, for example, esters of 17alpha-ethynyl-7alpha-methyl-1,3,5(10)-estratriene-1,3,17beta-triol (German patent 1 593 509 and German laid-open specification 2 818 164). Further, also the 14,17beta-ethano-14beta-estratrienes described in DE-A 36 28 189 as useful. The estrogenic and gestagenic active components are preferably administered together orally; but they can also be administered separately and/or parenterally or transdermally.

The agents of this invention can be used in the methods of this invention analogously to use of agents known for such purposes, e.g., those of EP 253607 but routinely taking into account the beneficial properties discussed herein.

The formulation of the preparations according to the invention based on 6beta, 7beta; 15beta, 16beta-dimethylene-3-oxo-4-androstene-[17(beta-1')-perhydrofuran-2'-one (I) is performed in a way known in the art by processing the active ingredient, optionally in combination with an estrogen, with the vehicles, diluents, optional flavorings, etc. common in galenicals, and converting it into the desired form of administration. For the preferred oral administration, tablets, coated tablets, capsules, pills, suspensions or solutions are especially suitable. For parenteral administration, in particular oily solutions, such as, for example, solutions in sesame oil, castor oil and cottonseed oil, are suitable. To increase solubility, solubilizers such as, for example, benzyl benzoate or benzyl alcohol, can be added.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius and unless otherwise indicated, all parts and percentages are by weight.

The entire disclosures of all applications, patents and publications, if any, cited above and below, and of corresponding application Federal Republic of Germany P 39 16 112.9, filed May 16, 1989, are hereby incorporated by reference.

EXAMPLES

Example 1

20.0 mg of 6beta, 7beta; 15beta, 16beta-dimethylene-3-oxo-4-androstene-[17(beta-1')-spiro-5']-perhydrofuran-2'-one and 0.05 mg of 17alpha-ethynylestradiol are mixed homogeneously with 140.45 mg of lactose, 59.5 mg of

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cornstarch, 2.0 mg of aerosil, 2.5 mg of polyvinylpyrrolidone 25 and 0.5 mg of magnesium stearate and pressed without advance granulation into a tablet of 225 mg final weight.

Example 2

Analogous to example 1, 10 mg of 6beta, 7beta; 15beta, 16beta-dimethylene-3-oxo-4-androstene-[17(beta-1')-spiro-5']-perhydrofuran-2'-one and 0.05 mg of 17alpha-ethynylestradiol with 150.45 mg of 17alpha-ethynylestradiol with 150.45 mg of lactose, 59.5 mg of cornstarch, 2.0 mg of aerosil, 2.5 mg of polyvinylpyrrolidone 25 and 0.5 mg of magnesium stearate are pressed into tablets with a final weight of 225 mg.

Example 3

Analogous to example 1, 20 mg of 6beta, 7beta; 15beta, 16beta-dimethylene-3-oxo-4-androstene-[17(beta-1')-spiro-5']-perhydrofuran-2'-one with 140.5 mg of lactose, 59.5 mg of cornstarch, 2.0 mg of aerosil, 2.5 mg of polyvinylpyrrolidone 25 and 0.5 mg of magnesium stearate are pressed into tablets with a final weight of 225 mg.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

What is claimed is:

1. A method of simultaneously achieving, during premenopause or menopause a gestagenic effect, antiandrogenic effect, and an antialdosterone effect in a female patient in need thereof comprising administering an amount of dihydrospirorenone to said female patient, wherein said amount of dihydrospirorenone is effective to simultaneously achieve a gestagenic effect, antiandrogenic effect and antialdosterone effect in said patient.
2. A method according to claim 1, wherein said patient is in premenopause.
3. A method of claim 2, wherein stabilization of menstruation is achieved.
4. A method according to claim 1, wherein said female is of age 35-55.
5. A method according to claim 1, wherein said patient is in menopause.
6. A method according to claim 1, wherein said effective amount of dihydrospirorenone is 0.5-50 mg per day.
7. A method according to claim 6, wherein said effective amount of dihydrospirorenone is 1-10 mg per day.
8. A method of claim 1, wherein said patient is predisposed to androgenization symptoms.
9. A method of claim 1, wherein said patient suffers from or is predisposed to high blood pressure.
10. A method of claim 2, wherein said patient suffers from or is predisposed to high blood pressure.
11. A method of simultaneously achieving, during premenopause or menopause, a contraceptive effect, an antiandrogenic effect, and an anti-aldosterone effect in a female patient in need thereof comprising administering an effective amount of dihydrospirorenone and an effective amount of an estrogenic compound, wherein said effective amount of dihydrospirorenone is effective to simultaneously achieve a

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gestagenic effect, anti-androgenic effect, and an anti-aldosterone effect in said female patient.

12. A method according to claim 11, wherein said effective amount of dihydrospirorenone is 0.5-50 mg per day and said effective amount of an estrogenic compound is an amount equivalent to 0.5-4.0 mg of estradiol valerate per day.

13. A method of claim 11, wherein said patient suffers from symptoms of androgenization.

14. A method of claim 11, wherein said patient suffers from or is predisposed to high blood pressure.

15. A method of claim 13, wherein said patient is in premenopause.

16. A method of claim 13, wherein said patient suffers from or is predisposed to high blood pressure.

17. A method of claim 11, wherein said estrogenic compound is a synthetic estrogen.

18. A method of claim 11, wherein said estrogenic compound is a natural estrogen.

19. A method according to claim 11, wherein said female is of age 35-55.

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20. A method of claim 11, wherein said estrogenic compound is a synthetic estrogen.

21. A method of claim 12, wherein said estrogenic compound is a natural estrogen.

22. A method of claim 11, wherein the estrogenic compound is 17 α -ethynylestradiol.

23. A method of claim 11, wherein said patient is in menopause.

24. A method according to claim 11, wherein said effective amount of dihydrospirorenone is 1-10 mg per day.

25. A method of claim 11, wherein said patient is predisposed to androgenization symptoms.

26. A method of claim 15, wherein stabilization of menstruation is achieved.

27. A method according to claim 11, wherein said effective amount of dihydrospirorenone is 0.5-50 mg per day and said effective amount of an estrogenic compound is an amount equivalent to 0.02-0.04 mg of 17 α -ethynylestradiol per day.

* * * * *



US005756490A

United States Patent [19]

Lachnit et al.

[11] Patent Number: **5,756,490**[45] Date of Patent: **May 26, 1998****[54] PHARMACEUTICAL COMBINATION
PREPARATION FOR HORMONAL
CONTRACEPTION**

4,921,843	5/1990	Pasquale	514/170
5,262,408	11/1993	Bergink	514/182
5,280,023	1/1994	Ehrlich et al.	514/177

[75] Inventors: Ursula Lachnit; Bernd Düsterberg,
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Primary Examiner—Kimberly Jordan
Attorney, Agent, or Firm—Millen, White, Zelano &
Branigan, P.C.

[73] Assignee: Schering Aktiengesellschaft, Berlin,
Germany

[57] ABSTRACT

[21] Appl. No.: **718,401**

[22] PCT Filed: **Mar. 30, 1995**

[86] PCT No.: **PCT/EP95/01190**

§ 371 Date: **Dec. 16, 1996**

§ 102(e) Date: **Dec. 16, 1996**

[87] PCT Pub. No.: **WO95/26730**

PCT Pub. Date: **Oct. 12, 1995**

[30] Foreign Application Priority Data

Mar. 30, 1994 [DE] Germany 44 11 585.7

[51] Int. Cl.⁶ **A61K 31/56**

[52] U.S. Cl. **517/170; 514/843**

[58] Field of Search **514/170, 843**

[56] References Cited**U.S. PATENT DOCUMENTS**

3,502,772	3/1970	Ijzerman	424/239
3,639,600	2/1972	Hendrix	424/242

A pharmaceutical combination preparation with two hormone components that are manufactured physically separately in a packaging unit and that are intended for time-sequential oral administration, which in each case consist of a number of daily dosage units that are placed physically separately and are individually removable in the packaging unit. As a hormonal active ingredient, a first hormone component contains in combination an estrogen preparation and, in at least a dosage that is sufficient to inhibit ovulation, a gestagen preparation, and as a hormonal active ingredient the second hormone component contains only an estrogen preparation. The first hormone component comprises 23 or 24 daily units and the second hormone component comprises 4 to 10 daily units. The total number of hormone daily units is equal to the total number of days of the desired cycle, but at least 28 days in length. This combination preparation is used for female birth control, and allows for an estrogen content that is as low as possible in each individual dosage unit and also has a low total hormone content per administration cycle, with high contraceptive reliability, low incidence of follicular development, and satisfactory cycle control, with reliable avoidance of intracyclic menstrual bleeding as well as of undesirable side-effects.

13 Claims, No Drawings

Novedad

Drospirenona + Ethinil estradiol

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**PHARMACEUTICAL COMBINATION
PREPARATION FOR HORMONAL
CONTRACEPTION**

DESCRIPTION

This invention relates to a pharmaceutical combination preparation with two hormone components which are manufactured physically separately in a packaging unit and are intended for oral administration that is sequential in time and which consist in each case of a number of physically separate and individually removable daily dosage units placed in the packaging unit, whereby as a hormonal active ingredient a first hormone component contains in combination an estrogen preparation and, in a dosage that is sufficient at least to inhibit ovulation, a gestagen preparation in either one-phase or multiple-phase structuring and as a hormonal active ingredient the second hormone component contains only an estrogen preparation, whereby the first hormone component comprises 23 or 24 daily units and the second hormone component comprises 4 to 8 daily units; the daily units of the first hormone component do not contain the combination of a biogenic estrogen and a synthetic estrogen, and the total number of hormone daily units is equal to the total number of days of the desired cycle, but at least 28-days in length, and a corresponding packing that contains this combination preparation.

Oral contraceptives in the form of combination preparations have been known as so-called one-phase preparations since 1960.

These preparations consist of 21 active ingredient-containing dosage units and 7 active ingredient-free tablets or coated tablets. The daily dosage unit consists of an estrogen and a gestagen. In one-phase preparations, the dose of the active substance that is to be administered daily is equally high in each dosage unit. If the dose of the active components that is to be administered daily is different in the individual dosage units in individual sections over the administration cycle, these are so-called multiple-phase preparations. Triquilar® can be cited as an especially well-known representative (DE-A 23 65 103).

The daily gestagen dosage has been continuously reduced through the development of new, more effective gestagens than those contained in the first oral contraceptives. It was also possible to lower, the daily estrogen dosage, although in most cases ethinylestradiol is still contained as an estrogen in hormonal contraceptives.

Because of the development of new, improved oral contraceptives, the following three points were (and are) emphasized:

- (1) Contraceptive reliability,
- (2) good cycle control, i.e., low incidence of intracyclic menstrual bleeding and
- (3) a minimum of undesirable side-effects are to be ensured.

Contraceptive reliability is mainly provided by the gestagen component. The amount of its daily dosage corresponds in each case to at least the maximum dose that is considered necessary for the gestagen in question to inhibit ovulation. The ethinylestradiol that is used in most cases as an estrogen in combination preparations is supposed to increase the ovulation-inhibiting effect of the gestagen and mainly to ensure cycle stability. The daily dose in the case of ethinylestradiol administered alone, which must be used to inhibit ovulation, is 100 µg.

Combination preparations with the most recent generation of gestagens are, e.g., the one-phase preparation Femovan

(DE-PS 2546062) or Marvelon (DE-OS 2361120). Milvane® can be mentioned (EP-0 148 724) as an example of a multiple-phase preparation whose dosage units contain a gestagen of the most recent generation, namely gestodene.

In the case of these three-phase preparations, in most cases 4-6 coated tablets are administered in the first phase, in which each coated-tablet contains an amount of estrogen in a low dose and a gestagen in a low dose. In the second phase of 4-6 coated tablets, each dosage unit contains an estrogen at a dose that is equal or slightly raised, increased to a maximum up to 2-fold, and a gestagen at a dose that is equal or slightly raised, increased to a maximum up to 1.5-fold. In a third phase of 9-11 units, each coated tablet contains an estrogen at a dose that is equal or is further raised, increased to a maximum of 3 times the initial value. Then come 7 pill-free days.

Recently, multiple-phase combination preparations were also proposed which can provide an extended, i.e., up to 24-day, intake of active ingredient-containing dosage units in a 28-day cycle. In this case, the daily gestagen-dosage amount either increases from the first through the second to the third phase (EP-A 0 491 415), or it decreases (EP-A 0 491 438). To complete the 28-day cycle, 4 blank pill days, 4 placebos, or else 4 exclusively gestagen-containing dosage units follow, or in the second case 4 to 7 blank pill days or 4 to 7 placebos follow.

The purpose of the development of new oral contraceptives with a reduced daily hormone dose was to minimize the side-effects that are described in epidemiological studies. Recent epidemiological data point to such a trend toward better compatibility of low-dosed preparations with respect to cardiovascular side-effects. [Thorogood M., Oral Contraceptives and Cardiovascular Disease: An Epidemiologic Overview; Pharmacoevidemiology and Drug Safety, Vol. 2: 3-16 (1993); 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); Lidegaard O., Oral Contraception and Risk of a Cerebral Thromboembolic Attack: Results of a Case-Control Study; BMJ Vol. 306, 956-63 (1993); Vessey M., Mant D., Smith A., Yeates D., Oral Contraceptives and Venous-Thromboembolism: Findings in a Large Prospective Study; BMJ, Vol. 292, (1986); Mishell D. R., Oral Contraception: Past, Present and Future Perspectives; Int J Fertile. 36 Suppl., 7-18 (1991)].

A correlation between the amount of the daily estrogen dose and the frequency of cardiovascular complications is assumed.

The preparation with the lowest-dosed amount of estrogen at this time is marketed as Mercilon® and contains 20 µg of ethinylestradiol in combination with 150 µg of desogestrel in each daily dosage unit over 21 days, followed by a 7-day pill-free interval. The cycle control of this preparation is somewhat less good than that of preparations with a higher estrogen dose. The observation, confirmed in several studies, of slighter ovarian suppression for the preparation that contains 20 µg of ethinylestradiol represents another clinically important problem. Obviously, for many women this very low estrogen dose can result in the maturation of follicles, as has been detected in ultrasound studies or hormone studies [Lunell N. O., Carlström K., Zador G., Ovulation Inhibition with a Combined Oral Contraceptive Containing 20 µg of Ethinylestradiol and 250 µg of Levonorgestrel; Acta Obstet Gynecol Scand Suppl. 88: 17-21 (1979); Mall-Haefeli M., Werner-Zodrow I. Huber P. R., Klinische Erfahrungen mit Mercilon und Marvelon unter

besonderer Berücksichtigung der Ovar-Funktion [Clinical Experiments with Mercilon and Marvelon with Special Consideration of Ovarian Function]; Geburtsh. und Frauenheilk. [Childbirth and Gynecology], 51, 35-38. Georg Thieme Verlag, Stuttgart-New York (1991); Strobel E., Behandlung mit oralen Kontrazeptiva [Treatment with Oral Contraceptives]; Fortschr. Med. 110 Jg. No. 20 (1992); Letter to Editor, Contraception 45: 519-521 (1992);

Teichmann A. T., Brill K., Can Dose Reduction of Ethinylestradiol in OCs Jeopardize Ovarian Suppression and Cycle Control? Abstract Book, VIIIth World Congress on Human Reproduction, Bali, Indonesia (1993)].

Until recently, a multiple-day break in the intake of coated tablets that contain active ingredients was deemed necessary to trigger withdrawal bleeding and to ensure adequate cycle control.

Other preparations have been described which contain an estrogenic and a gestagenic active ingredient and which generally are administered over 21 days in constant amounts in each individual dosage unit, in which the intake of this dosage unit that contains an estrogenic and gestagenic active ingredient precedes the intake of exclusively estrogen-containing dosage units (Ijzerman, US-A 3.502.772; Pasquale, US-A 4.921.843; Kuhl et al., EP-A 0 499 348). In the case of these preparations, the patient begins taking dosage units that contain only one estrogenic active ingredient, specifically at a dosage that lies below the ovulation-inhibiting dose of the estrogenic component, which can lead to follicular development, either as early as on the first cycle day (Kuhl) or at the earliest on the second cycle day (Pasquale). Follicular development is thought to be responsible for breakthrough ovulations (Chowdhury et al., "Escape" Ovulation in Women Due to the Missing of Low-Dose Combination Oral Contraceptive Pills, Contraception, 22: 241-247, 1980; Molloy B. G. et al., "Missed Pill" Conception: Fact or Fiction? Brit. Med. J. 290, 1474-1475, 1985). Contraceptive protection is thus jeopardized. The risk of pregnancy is therefore high, especially in the case of intake errors below the 20 µg ethinylestradiol preparations.

From DE-PS 43 08 406 (not republished), an ovulation-inhibiting agent in the form of a combination preparation for contraception is already known, in which at least one hormone component that contains both estrogen and gestagen is provided, in which the daily units contain both a biogenic estrogen and a synthetic estrogen. This invention does not relate to such preparations.

The object of this invention is to make available a combination preparation with an estrogen content that is as low as possible in each individual dosage unit but also with a low total hormone content per administration cycle, whereby with high contraceptive reliability, an incidence of follicular development that is as low as possible and satisfactory cycle control with reliable avoidance of intracyclic menstrual bleeding such as breakthrough bleeding and "spottings" are to be achieved and undesirable side-effects are to be avoided.

This object is achieved by the provision of the above-indicated two-phase combination preparation.

According to this invention, preferred are combination preparations whose first hormone component comprises 24 daily units and whose second hormone component comprises 4 to 8 daily units.

In the first phase, beginning with the first day of the cycle, a dosage unit that contains an estrogen in combination with a gestagenic component is administered daily over 23 or 24 days. After that is the second phase, in which an estrogen is administered over 5 days or 4 days over the remaining period in the cycle, which also comprises 28 days.

In the preferred case, 24 daily dosage units that contain an estrogen and a gestagen preparation, as well as 4 daily dosage units that contain only an estrogen preparation, are administered.

In this case, the first phase which contains both estrogen and gestagen can also be structured in multiple phases, for example, in three phases, in a way that is familiar to one skilled in the art (in this connection, see, for example, EP-A 0 148 724). Such a preparation is then referred to as a four-phase preparation.

The one-phase structure of the first hormone component is preferred, however.

When the combination preparation according to the invention is taken, the recruitment of the dominant follicle, which in the spontaneous cycle occurs during the first 6 days of the menstrual cycle, is already efficiently suppressed in the first administration cycle. Thus, with the combination preparation of this invention, follicular development can be suppressed as early as in the first intake cycle, and thus breakthrough ovulations can be avoided, thereby increasing contraceptive reliability.

This is of eminent importance mainly in the case of intake errors, namely especially with hormonal contraceptives with low daily ethinylestradiol dose amounts. Since, in the case of 25% of women who take the pill, intake errors (skipping dosage units or extending the interval between the daily intake of two dosage units to more than 24 hours) are known (Finlay I. G., Scott M. B. G.: Patterns of Contraceptive Pill-taking in an Inner City Practice. Br. Med. J. 1986, 293: 601-602), the combination preparation according to the invention, if it is used as an ovulation-inhibiting agent, increases contraceptive reliability. This is true especially in the case of lowest-dosed preparations.

The increase in the number of dosage units above the usual number of 21 days to 23 or 24 days produces an effective shortening of the pill-free interval, in which the selection of follicles occurs with conventional combination preparations as in a normal menstrual cycle, and thus follicular development results and increased endogenous estrogen is formed. These follicles lead to breakthrough ovulations, as already stated above. These breakthrough ovulations occur to an increased extent especially in the case of intake errors.

The subsequent phase, in which dosage units that contain only one estrogenic component as a hormonal active ingredient are administered daily over 4 to 8 days, ensures withdrawal bleeding and produces stimulation of progesterone receptors in the endometrium, thus ensuring in the subsequent administration cycle a reduced rate of intracyclic menstrual bleeding compared with conventional, low-dosed preparations.

According to a preferred embodiment of the invention, the estrogen of the first hormone component is selected from the group of compounds

17β-estradiol,
ethinylestradiol and
17β-estradiol valerate

and the gestagen is selected from the group of compounds

gestodene,
levonorgestrel,
desogestrel,
3-ketodesogestrel,
drospironone,
cyproterone acetate,
norgestimate and
norethisterone and

the estrogen of the second hormone component is selected from the group of compounds

17β-estradiol,
ethinylestradiol and
17β-estradiol valerate.

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According to another preferred variant of this invention, the estrogen of the first hormone component in each daily dosage unit is contained in a dose of

1.0 to 6.0 mg of 17 β -estradiol.

0.01 to 0.04 mg of ethinylestradiol.

1.0 to 6.0 mg of 17 β -estradiol valerate and the gestagen in each daily dosage unit is contained in a dose of

0.04 to 0.075 mg of gestodene.

0.05 to 0.125 mg of levonorgestrel.

0.06 to 0.15 mg of desogestrel.

0.06 to 0.15 mg of 3-ketodesogestrel.

1.0 to 3.0 mg of drospironenone.

1.0 to 2.0 mg of cyproterone acetate.

0.2 mg to 0.3 mg of norgestimate.

0.35 to 0.75 mg of norethisterone.

As the daily amounts in the daily units of the first hormone component, 0.015 to 0.025 mg is especially preferred for ethinylestradiol, 1.0 to 4.0 mg is especially preferred for 17 β -estradiol valerate, and 0.05 to 0.075 mg is especially preferred for gestodene.

The second hormone component contains the estrogen in each daily dosage unit preferably in an amount of

1.0 to 6.0 mg of 17 β -estradiol.

0.002 to 0.04 mg of ethinylestradiol.

1.0 to 6.0 mg of 17 β -estradiol valerate.

According to an especially preferred embodiment, the second hormone component in each daily dosage unit contains, as estrogen, ethinylestradiol in an amount of 0.01 to 0.025 mg, 17 β -estradiol in an amount of 1.0 to 3.0 mg, or 17 β -estradiol valerate in an amount of 1.0 to 4.0 mg.

A preparation according to this invention contains a total of preferably 28 hormone daily units.

As an estrogen for both the first and the second hormone component, primarily ethinylestradiol or 17 β -estradiol is considered.

Of the above-mentioned gestagens for the first hormone component, gestodene is to be emphasized; also levonorgestrel is preferred.

17 β -estradiol, which can be contained as estrogen both in the first and in the second hormone component, is mentioned only as a possible representative of this 17 β -estradiol ester; other such homologous esters can also be used as estrogenic components within the scope of this invention.

The following example is used to explain this invention in more detail:

EXAMPLE 1:

Day	1	2	3	4	5	6	7
Composition	C	C	C	C	C	C	C
Day	8	9	10	11	12	13	14
Composition	C	C	C	C	C	C	C
Day	15	16	17	18	19	20	21
Composition	C	C	C	C	C	C	C
Day	22	23	24	25	26	27	28
Composition	C	C	C or E	E	E	E	E

Day=Day of the menstrual cycle, day 1 is the first day of bleeding

C=combination of estrogen and gestagen (=first hormone component)

E=estrogen (=second hormone component).

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The dosage units are formulated conventionally using estrogen-/gestagen- and exclusively estrogen-containing tablets, pills, coated tablets, etc. of known adjuvants for production.

The number of daily units in the individual phases within the first hormone component in the case of the structure of the combination preparation according to the invention as a four-phase preparation is indicated below:

	1st Phase	2nd Phase	3rd Phase	4th Phase
Number of daily units	4 to 9 C1	4 to 9 C2	9 to 13 C3	E = 28 - (C1 + C2 + C3)

C1, C2, C3=combination gestagen and estrogen within the first hormone component

According to the invention, the estrogen/gestagen dosage ratios in the daily dosage units of the individual phases should lie within the ranges indicated below. In this case, the dosage in the first phase is set as 1, and the dose ranges in the following phases are indicated as multiples of the dosage in the first phase:

	1st Phase	2nd Phase	3rd Phase	4th Phase
estrogen	1	1-2	0.5-1.5	0.5-1
gestagen	1	1-1.5	1.5-3	—

The composition of a combination preparation according to the invention in four-phase structure can be seen in the example below:

	1st Phase	2nd Phase	3rd Phase	4th Phase
Number of daily units	5 C1	7 C2	12 C3	4 E
ethinylestradiol [mg] or 17 β -estradiol [mg]	0.020	0.025	0.020	0.010
gestodene [mg] or levonorgestrel [mg]	2.000	3.000	2.000	1.000
	0.050	0.060	0.070	—
	0.050	0.075	0.100	—

The combination preparation according to the invention is used in female contraception by administering the daily dosage units of the first hormone component over 23 or 24 days, beginning on day one of the menstrual cycle (first day of menstrual bleeding), followed by 4 to 8 daily dosage units that contain exclusively one estrogen (E), during a total of at least 28 days in the administration cycle. With this combination preparation, pronounced ovarian suppression without frequent follicle stimulation can be achieved, as well as excellent cycle control in the case of low daily estrogen dosage, low total amounts of estrogen, and low total amounts of hormone per administration cycle.

The advantages of this combination preparation (ovulation-inhibiting agent) according to the invention that is administered over generally 28 days compared to the previously described preparations, especially those with a daily ethinylestradiol dose of less than 30 μ g and those with a pill-free interval, can be characterized as follows:

1. A significantly lower frequency of follicular development in the user. This means a lower risk of breakthrough

- ovulation and thus greater contraceptive reliability, especially in the case of intake errors.
- The recruitment of the dominant follicle is suppressed as early as in the first cycle by extending the intake of the combination to 23 or 24 days.
 - The intake of 4 to 8 daily estrogen dosage units each in connection with the administration of the 23- or 24-day combination dosage results in considerably improved cycle control and a lower incidence of side-effects, such as headaches, within the framework of the premenstrual syndrome.
 - Other clinical symptoms that are attributable to greatly fluctuating endogenous estrogen levels, such as, for example, breast tenderness, are reduced also clearly 0.015 to 0.025 mg owing to the considerably greater ovarian suppression.

The above-mentioned advantages, especially the suppression of follicular development and the accompanying inhibition of endogenous estrogen production, are more pronounced in the case of the combination preparations according to the invention, which comprise 24 daily units of the first hormone component and thus, as mentioned above, the latter are preferred.

The formulation of an estrogen and a gestagen for the production of a combination preparation according to the invention is carried out completely analogously to the way already known for conventional oral contraceptives with a 21-day intake period of the active ingredients, such as, for example, Femovan® (ethinylestradiol/gestodene) or Microgynon® (ethinylestradiol/levonorgestrel). The formulation of the dosage units that contain only estrogen can also be carried out quite analogously to the way known for already obtained estrogen-containing agents that are intended for oral use, for example, Progynon C®.

A packing that contains a combination preparation according to the invention is also built up analogously to packings for already known oral contraceptives that are on the market, with the difference that, instead of the usual 21 dosage units that contain active components, now 23 or 24 such dosage units and another 4 to 8 dosage units that contain only estrogen are present. As a packaging form for the combination preparation according to the invention, generally a conventional blister pack is used, but other packaging forms that are known for this purpose are also conceivable.

In addition, the invention relates to a process for female contraception in which the above-described combination preparation is administered in the indicated way.

To determine equivalent-action amounts of ethinylestradiol and 17 β -estradiol, on the one hand, and various gestagens such as gestodene, levonorgestrel, desogestrel and 3-ketodesogestrel, on the other hand, reference is made to the indications given in EP-A-0 253 607. Other details for determining dose equivalents of various gestagenic active ingredients are found in, for example, "Probleme der Dosisfindung: Sexualhormone [Problems of Dose Finding: Sex Hormones]"; F. Neumann et al., in "Arzneimittelforschung [Pharmaceutical Agent Research]" (Drug Research) 27, 2a, 296-318 (1977) as well as in "Aktuelle Entwicklungen in der hormonalen Kontrazeption [Current Developments in Hormonal Contraception]"; H. Kuhl in "Gynäkologie [Gynecologist]" 25: 231-240 (1992).

We claim:

1. Pharmaceutical combination preparation with two hormone components that are manufactured physically separately in a packaging unit and that are intended for time-sequential oral administration, which in each case consist of

a number of daily dosage units that are placed physically separately and individually removable in the packaging unit, whereby as a hormonal active ingredient a first hormone component contains in combination an estrogen preparation and in at least a dosage that is sufficient to inhibit ovulation a gestagen preparation in either a one-phase or multiple-phase structure and as a hormonal active ingredient the second hormone component contains only an estrogen preparation, whereby the first hormone component comprises 23 or 24 daily units and the second hormone component comprises 4 to 10 daily units, the daily units of the first hormone component do not contain the combination of a biogenic estrogen and a synthetic estrogen, and the total number of hormone daily units is equal to the total number of days of the desired cycle, but at least 28 days in length.

2. Combination preparation according to claim 1, wherein the estrogen of the first hormone component is selected from the group of compounds

17 β -estradiol,

ethinylestradiol and

17 β -estradiol valerate and the gestagen is selected from the group of compounds

gestodene,

levonorgestrel,

desogestrel,

3-ketodesogestrel,

drospironenone,

cyproterone acetate,

norgestimate and

norethisterone and

the estrogen of the second hormone component is selected from the group of compounds

17 β -estradiol,

ethinylestradiol and

17 β -estradiol valerate.

3. Combination preparation according to claim 2, wherein the estrogen of the first hormone component in each daily dosage unit is contained in a dose of

1.0 to 6.0 mg of 17 β -estradiol,

0.015 to 0.025 mg of ethinylestradiol, and

1.0 to 4.0 mg of 17 β -estradiol valerate

and the gestagen in each daily dosage unit is contained in a dose of

0.05 to 0.075 mg of gestodene,

0.05 to 0.125 mg of levonorgestrel,

0.06 to 0.15 mg of desogestrel,

0.06 to 0.15 mg of 3-ketodesogestrel,

1.0 to 3.0 mg of drospironenone,

1.0 to 2.0 mg of cyproterone acetate,

0.2 mg to 0.3 mg of norgestimate and

0.35 to 0.75 mg of norethisterone.

4. The combination preparation of claim 3, wherein the second hormone component contains, in each daily dosage unit, an amount of:

1.0 to 6.0 mg of 17 β -estradiol,

0.002 to 0.04 mg of ethinylestradiol, and

1.0 to 4.0 mg of 17 β -estradiol valerate.

5. Combination preparation according to claim 2, wherein the second hormone component contains, in each daily dosage unit, an amount of

1.0 to 6.0 mg of 17 β -estradiol,

0.002 to 0.04 mg of ethinylestradiol, and

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1.0 to 4.0 mg of 17 β -estradiol valerate.

6. Combination preparation according to claim 5, wherein the second hormone component in each daily dosage unit contains ethinylestradiol in an amount of 0.01 to 0.025 mg.

7. The combination preparation of claim 2, wherein the second hormone component contains, in each daily dosage unit, an amount of:

1.0 to 3.0 mg of 17 β -estradiol,

0.01 to 0.025 mg of ethinylestradiol, and

1.0 to 4.0 mg of 17 β -estradiol valerate.

8. Combination preparation according to claim 1, wherein the total number of hormone daily units is 28.

9. The combination preparation according to claim 1, wherein the first hormone component has 24 daily units and the second hormone component has 4-8 daily units.

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10. The combination preparation according to claim 1, wherein the first hormone component has 24 daily units and the second hormone component has 4 daily units.

11. The combination preparation of claim 1, wherein the estrogen in both the first and second hormone components is selected from ethinylestradiol or 17 β -estradiol.

12. The combination preparation of claim 1, wherein the gestagen in the first hormone component is selected from gestodene or levonorgestel.

13. The combination preparation of claim 1, wherein the first hormone component has three phases of daily units wherein the estrogen and/or the gestagen amounts differ between phases.

* * * * *

ANEXO 5

PCT

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(54) Title: PROGESTIN/ESTROGEN ORAL CONTRACEPTIVE

(57) Abstract

This invention provides a method of contraception which comprises administering to a female of child-bearing age a combination of a progestin at a daily dosage of 40-500 μ g trimegestone, 250 μ g - 4 mg dienogest, or 250 μ g - 4 mg drospirenone, and an estrogen at a daily dosage equivalent in estrogenic activity to 10-20 μ g ethinyl estradiol for 23-25 days beginning on day 1 of the menstrual cycle; wherein the same dosage of the progestin and estrogen combination is administered in each of the 23-25 days, followed by the administration of an estrogen at a daily dosage equivalent in estrogenic activity to 5-15 μ g ethinyl estradiol for 3-5 days; wherein the same dosage of the estrogen is administered in each of the 3-5 days; such that the number of days of administration of the progestin and estrogen combination plus the number of days of administration of estrogen is equal to 28 per menstrual cycle.

Novedad.

Ethinil-estradiol + Drospirenona.

PROGESTIN/ESTROGEN ORAL CONTRACEPTIVE

BACKGROUND OF THE INVENTION

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The vast majority of oral contraceptives consist of a combination of a progestin and estrogen that are administered concurrently for 21 days followed either by a 7 day pill free interval or by the administration of a placebo for 7 days in each 28 day cycle. The most important aspects of a successful oral contraceptive product are effective
10 contraception, good cycle control (absence of spotting and breakthrough bleeding and occurrence of withdrawal bleeding), and minimal side effects. Combination oral contraceptives have traditionally acted by suppression of gonadotropins. In addition, it appears that the progestin component is primarily responsible for contraceptive efficacy through inhibition of ovulation, and other peripheral effects which include changes in
15 the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation). The estrogenic component intensifies the anovulatory effect of the progestin, and is also important for maintaining cycle control.

Since the introduction of oral contraceptives (OCs) over a quarter-century ago,
20 research has been directed toward developing preparations that minimize the potential for side effects while maintaining efficacy and normal menstrual patterns. The first-generation OCs contained more progestin and estrogen than was necessary to prevent conception. Adverse hemostatic and metabolic changes, clinical problems, and side effects were associated with these high-dose preparations. In 1978, the World Health
25 Organization (WHO) recommended that the focus of OC research should be the development of products containing the lowest possible dose levels of estrogen and progestin.

The first reductions in steroid content in a combination pill were focused on estrogen because it, rather than progestin, was thought to be related to the most serious
30 side effects. Reduction in progestin content followed, as evidence mounted that lowering progestin intake might lower the risk of cardiovascular complications such as stroke and ischemic heart disease. [Kay CR, Am J Obstet Gynecol 142:762 (1982)]. However, this evidence was not as clear as that implicating estrogen in thromboembolic disorders. [Inman WHW, Br Med J 2:203 (1970); Stolley PD, Am J Epidemiol
35 102:197 (1975)]. The need for a balance between estrogens and progestins to minimize adverse effects on carbohydrate metabolism and on lipid and lipoprotein levels was also

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recognized. [Bradley DD, N Engl J Med 299:17 (1978); Wynn V, Lancet 1:1045 (1979)]. Researchers then found that the synergistic action between progestin and estrogen in a balanced ratio successfully inhibited ovulation at low levels of both components.

5 Research into low-dose progestins was advanced significantly by the development of norgestrel (Ng) and levonorgestrel (LNg). Levonorgestrel is the biologically active moiety of racemic norgestrel. It is strongly progestational, has no inherent estrogenic activity, is antiestrogenic, and possesses good biologic activity. The contraceptive effects of levonorgestrel are manifested throughout the hypothalamic-pituitary-gonadal-target organ axis.

10 Ethinyl estradiol (EE) is the estrogen most frequently used in combination OCs. In attempts to fulfill the WHO objective, the dosage of EE in marketed OC formulations has been steadily reduced from that found in earlier OCs. Thromboembolic mortality decreased when the amount of synthetic estrogen in OC formulations was reduced from
15 100 µg to 50 µg. Subsequently, a significant reduction in fatal myocardial infarctions was reported for women using OCs with 30 µg of EE rather than 50 µg of EE. [Meade TW, Br Med J 280:1157 (1980)].

 In keeping with the goal of reducing the total steroidal dosage, while maintaining contraceptive efficacy, good cycle control, and minimizing side effects,
20 numerous regimens have been developed in which the progestin/estrogen combination is administered either as a fixed dosage combination (monophasic) or as biphasic or triphasic regimens in which the dosage of the combination is varied either once or twice throughout the menstrual cycle. In these regimens, the progestin/estrogen combination is typically administered for 21 days followed by either a 7-day pill free period or the
25 administration of a non-contraceptive placebo (or iron supplement) for 7 days. In these regimens, 3-ketodesogestrel (3-KDSG), desogestrel (DSG), levonorgestrel (LNg), gestodene (GTD), norgestrel (NG), and norethindrone (NE) are typically used as the progestin while ethinyl estradiol (EE); 17β-estradiol, and mestranol are typically the estrogenic components. Other progestins less frequently used include drospirenone
30 (DRSP) and dienogest (DGST).

 An oral contraceptive product containing a combination of 3 mg DGST and 30 µg EE for 21-day administration per cycle is marketed in Germany.

 Several examples of attempts at reducing the total steroidal dosage are provided below.

35 Lachnit (PCT Publication WO 95/26730) discloses bridged regimens consisting of the administration of a combination of a progestin/estrogen combination (50 - 125 µg

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LNg and 10 - 40 µg EE) for the first 23-24 days of the menstrual cycle followed by the administration of an estrogen (2 - 40 µg EE) for 4-10 days for a total administration of at least 28 days per cycle. The use of 100 - 300 µg drospirenone and 10 - 40 µg EE as the 23-24 day progestin/estrogen combination is disclosed. Lachnit also discloses a
5 triphasic plus bridging regimen (4-9 days, 4-9 days, 9-13 days, and 28 days for the three phases and estrogen phase, respectively) in which a combination of 50 µg LNg and 20 µg EE are administered in the first phase, a combination of 75 µg LNg and 25 µg EE are administered in the second phase, a combination of 100 µg LNg and 20 µg EE are administered in the third phase, and 10 µg EE is administered in the estrogen
10 phase. Other progestins disclosed include GTD, DSG, 3-KDSG, DRSP, cyproterone acetate, norgestimate, and norethisterone.

Erlich (German Patent DE 4,104,385 C1 and U.S. Patent 5,280,023) discloses sequential contraceptive regimens consisting of the administration of an estrogen which effects a disturbance of follicle stimulation, followed by the administration of a
15 combination of a progestin/estrogen in a dose at least adequate to inhibit ovulation. The regimen is administered for a total of 28 days per cycle. It is preferred that the estrogen is administered for 5-14 days per cycle and the progestin/estrogen combination is administered for 23-14 days per cycle, so that the total administration is for 28 days per cycle. Specific regimens include (a) 4 mg estradiol for 7 days followed by 21 days
20 of the combination of 1 mg norethisterone acetate and 4 mg estradiol; (b) 2 mg estradiol valerate for 7 days followed by 21 days of the combination of 2 mg chlormadinone acetate and 4 mg estradiol valerate; and (c) 20 µg EE followed by 18 days of the combination of 150 µg LNg and 20 µg EE. Regimen (c) in Erlich provides a total steroidal load of 2.7 mg of LNg and 560 µg EE per 28 day cycle.

25 Moore (DE 4313926 A1) discloses bridged triphasic regimens consisting of the administration of a combination of 10 - 50 µg LNg and 5 - 20 µg EE from days 1-7 of the menstrual cycle; of 50 - 75 µg LNg and 5 - 20 µg EE from days 8-14 of the menstrual cycle; of 75 - 125 µg LNg and 5 - 20 µg EE from days 15-21 of the menstrual cycle; and 5 - 20 µg EE from days 22-28 of the menstrual cycle.

30 Oettel (EP 696,454 A2) discloses a three phase contraceptive regimen in which the first phase consists of the administration for 3-4 days of a composition containing at least one biogenic estrogen; the second phase consists of the administration for 20-22 days of at least one biogenic estrogen and at least one progestin (progesterone, DGST, desogestrel, 3-KDSG, GTD, LNg, norgestimate, norethisterone, norethisterone acetate,
35 dehydrogestrone, chlormadinone acetate, cyproterone acetate, medroxyprogesterone

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acetate, or megestrol acetate); and the third phase consists of the administration for 3-4 days of a composition containing at least biogenic one estrogen.

Spona (PCT Publication WO 95/17194) discloses contraceptive regimens which consist of the administration of a combination of a progestin (50 - 75 µg GTD, 75 - 125 µg LNg, 60 - 150 µg DSG, 60 - 150 µg 3-KDSG, 100 - 300 µg DRSP, 100 - 200 µg cypoterone acetate, 200 - 300 µg norgestimate, or >350 - 750 µg norethisterone) and an estrogen (15 - 20 µg EE or 2 - 6 mg 17β-estradiol) for 23-24 days per cycle.

Oettel (EP 628,312 A1) discloses combination contraceptive combinations containing the combination of three components: a biogenic estrogen (estradiol, estrone, or estriol), a synthetic estrogen (EE or mestranol), and a progestin (LNg, desogestrel, progesterone, norethisterone acetate, DGST, chlormadinone acetate, gestodene, or cypoterone acetate). In one embodiment, the combination is administered for 21 days followed by the administration of placebo (or pill free) or an estrogen on days 22-28 of the cycle.

Upton (EP Patent Specification 253,607 B1) teaches the use of low dose progestin/estrogen combinations for combined hormone replacement therapy and contraception in climacteric women. Climacteric women are defined in Upton as premenopausal women around 40 years of age whose hormone levels are waning. The climacteric woman still ovulates (albeit may have irregular ovulation), but she still experiences many of the symptoms of the hypoestrogenic menopausal woman, such as insomnia, hot flushes, and irritability. Upton teaches the administration of a 23-26 day monophasic regimen of progestin/estrogen followed by a pill free or placebo interval of 2-5 days; with 24 days of progestin/estrogen administration followed by a 4-day pill free or placebo administration being preferred. Upton teaches the use of a progestin selected from 25 - 100 µg LNg, 10 - 70 µg GTD, 25 - 100 µg DSG, 25 - 100 µg 3-KDSG, and 85 - 350 µg NE used in combination with an estrogen selected from 500 - 2000 µg 17β-estradiol, 8 - 30 µg EE, and 15 - 60 µg mestranol. Based on relative potencies, Upton teaches that a dose of 75 µg LNg is equivalent to 35 µg of GTD, 75 µg of 3-KDSG or DSG, and 250 µg NE and that a dose of 1000 µg of 17β-estradiol is equivalent to a dose of 15 µg EE and 30 µg mestranol. Upton also teaches that NG may be substituted for LNg, but at twice the dose.

Sartoretto (Clinica e Terapeutica 3: 399 (1974)) discloses a monophasic contraceptive regimen consisting of the administration of a combination 100 µg LNg and 20 µg EE for 21 days.

Lachnit-Fixson (U.S. Patent 3,969,502) discloses biphasic progestin/estrogen combination regimens in which a combination of 50-125 µg LNg and 25-35 µg EE are

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administered for 10-12 days in the first phase and 100-350 µg LNg and 30-50 µg EE are administered for 10-12 days in the second phase. Placebo is administered for 5-7 days following the administration of the contraceptive steroid regimen.

5 Lachnit-Fixson (U.S. Patent 3,957,982) discloses triphasic 21-day progestin/estrogen regimens in which a combination of 40-90 µg LNg and 20-50 µg EE is administered for 4-6 days in the first phase, 50-125 µg LNg and 30-50 µg EE is administered for 4-6 days in the second phase, and 100-250 µg LNg and 25-50 µg EE is administered for 9-11 days in the third phase. It is preferred that the first, second, and third phases are 6, 5, and 10 days, respectively.

10 Bennick (U.S. Patent 5,418,228) discloses triphasic regimens which consist of the administration of a combination progestin/estrogen in a 6-8 day phase, a second 6-8 day phase, and a third 6-8 day phase, with it being preferred that the three contraceptive steroid phases be 7 days each. Bennick discloses that the first contraceptive steroid phase consists of a progestin at a daily dosage equivalent to 75 - 150 µg DSG and an
15 estrogen at a daily dosage equivalent to 20 - 25 µg EE; the second contraceptive steroid phase consists of a progestin at a daily dosage equivalent to 75 - 125 µg DSG and an estrogen at a daily dosage equivalent to 20 µg EE; and the third contraceptive steroid phase consists of a progestin at a daily dosage equivalent to 75 - 100 µg DSG and an estrogen at a daily dosage equivalent to 20 µg EE. Placebo is administered for 7
20 days following the 21-day contraceptive steroid period. Bennick discloses that the progestin may be 3-KDSG, DSG, LNg, or GTD.

Bergink (U.S. Patent 5,262,408) discloses a 24 day triphasic combination regimen in which the first 7-9 day phase consists of the administration of a progestin at a daily dosage equivalent to 100 µg DSG and an estrogen at a daily dosage equivalent to
25 25 µg EE, the second 7-9 day phase consists of the administration of a progestin at a daily dosage equivalent to 125 µg DSG and an estrogen at a daily dosage equivalent to 20 µg EE, and the third 7-9 day phase consists of the administration of a progestin at a daily dosage equivalent to 50 µg DSG and an estrogen at a daily dosage equivalent to 20 µg EE. It is preferred that the three phases be 8 days each. Following the 24 day
30 contraceptive steroid administration, a placebo may be administered for 4 days, the 4 day interval may be pill free, or a progestin at a dosage equivalent to 25-35 µg DSG may be administered.

Boissonneault (U.S. Patent 4,962,098) discloses triphasic progestin/estrogen combinations in which the amount of the estrogenic component is increased stepwise
35 over the three phases. Contraceptive steroid combinations are taken for 4-7 days during

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the first phase (5 days being preferred); for 5-8 days during the second phase (7 days preferred); and for 7-12 days during the third phase (9 days being preferred). Following the administration of 21-days of the contraceptive steroid combination, placebo is taken for 7 days. For all three phases, 0.5-1.5 mg of norethindrone acetate is used in the progestin, with 1 mg being preferred. 10-30 µg EE is used in the first phase, 20-40 µg in the second, and 30-50 µg in the third phase.

Pasquale (U.S. Patent 4,921,843) discloses combination progestin/estrogen contraceptive regimens which contain 0.5 to 1 mg of progestin and an estrogen having a dose equivalent to 10-40 µg of EE. NE, LNg, D-17β-acetoxy-13β-ethyl-17α-ethinylgon-4-en-3-one oxime, and 19-nor-17-hydroxy progesterone ester are disclosed as progestins, with NE being preferred. Specifically disclosed regimens include a uniphasic regimen (2 days of placebo, 5 days of 20 µg EE, and 21 days of a combination of 500 µg NE and 35 µg EE); a uniphasic regimen (2 days of placebo, 5 days of 40 µg EE, and 21 days of a combination of 500 µg NE and 35 µg EE); and a triphasic regimen (2 days of placebo; 5 days of 20-40 µg EE; 7 days of a combination of 500 µg NE and 35 µg EE; 7 days of a combination of 750 µg NE and 35 µg EE; and 7 days of a combination of 1 mg NE and 35 µg EE).

Pasquale (U.S. Patent 4,628,051) discloses triphasic progestin/estrogen combination regimens in which contraceptive steroid is administered for 21 days. Contraceptive steroid combinations are taken for 5-8 days during the first phase (7 days being preferred); for 7-11 days during the second phase (7 days preferred); and for 3-7 days during the third phase (7 days being preferred). In all three phases, an estrogen at a daily dosage equivalent to 20-50 µg EE is administered in combination with a progestin having a daily dosage equivalent to 65-750 µg NE in the first phase, 0.25-1.0 mg NE in the second phase, and 0.35-2.0 mg NE in the third phase. A specific triphasic regimen discloses the administration of 35 µg EE in each of the three 7-day phases in combination with 0.5 mg, 0.75 mg, and 1.0 mg in the first, second, and third phases, respectively. A second specific triphasic regimen discloses the administration of 35 µg EE in each of the three 7-day phases in combination with 50 µg, 75 µg, and 100 µg in the first, second, and third phases, respectively. A third specific triphasic regimen discloses the administration of 35 µg EE in each of the three 7-day phases in combination with 25 µg, 35 µg, and 50 µg in the first, second, and third phases, respectively.

Lachnit-Fixson (U.S. Patent 4,621,079) discloses triphasic 21-day progestin/estrogen combination regimens in which a combination of 40-70 µg GTD and 20-35 µg EE is administered for 4-6 days in the first phase; 50-100 µg GTD and

30-50 µg EE is administered for 4-6 days in the second phase; and 80-120 µg GTD and 20-50 µg EE is administered for 9-11 days in the third phase. Placebo is administered for 7 days following the 21-day contraceptive steroid regimen.

Pasquale (U.S. Patent 4,530,839) discloses triphasic 21-day progestin/estrogen combination regimens in which a dose of 20-50 µg EE is administered in all three phases in combination with a contraceptively effective daily dose of progestin in the first phase, 1.5-2 times that dose of progestin in the second phase, and 2-2.5 times the first phase dose of progestin in the third phase. Each of the three phases is 7 days long. A specific regimen discloses 20-50 µg EE in combination with 500 µg LNg, 750 µg LNg, and 1 mg LNg during each of the three 7-day phases, respectively.

Edgren (U.S. Patent 4,390,531) discloses triphasic 21-day progestin/estrogen combination regimens in which a dose of 20-40 µg EE (or another estrogen in an equivalent dosage) is administered in all three phases in combination with 0.3-0.8 mg NE (or another progestin in an equivalent dosage) for 5-8 days in the first phase, twice the dose of NE for 7-11 days in the second phase, and the dose of NE being the same as in the first phase for 3-7 days in the third phase. It is preferred that each of the three phases is 7 days. Placebo is administered for 6-8 days following administration of the contraceptive steroid combination. A specific regimen discloses a first phase of 7 days of 0.5 mg NE in combination with 35 µg EE, a second 7 day phase of 1.0 mg NE in combination with 35 µg EE, and a third 7 day phase of 0.5 mg NE in combination with 35 µg EE.

DESCRIPTION OF THE INVENTION

This invention provides a bridged monophasic combination progestin/estrogen oral contraceptive regimen for females of child-bearing age that provides effective contraception, good cycle control, and minimal side effects while greatly reducing the total contraceptive steroid administered (particularly the estrogenic component) per 28-day cycle. To achieve the substantial reduction in the total contraceptive steroid administered per cycle while maintaining good cycle control, the low dose progestin/estrogen combination is administered for 23-25-days per cycle followed by the administration of an estrogen for the remaining 3-5 days of the cycle. Administration of the contraceptive progestin/estrogen combination is begun on the first day of menses (day 1), and continued for 23-25 consecutive days. Following the 23-

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25-day administration period, an estrogen is administered for 3-5 days to assist in maintaining good cycle control. The total administration during each cycle is 28 days.

More particularly, this invention provides a method of contraception which comprises administering to a female of child bearing age a combination of 40-500 μ g
5 trimegestone, 250 μ g - 4 mg dienogest, or 250 μ g - 4 mg drospirenone, and an estrogen at a daily dosage equivalent in estrogenic activity to 10-20 μ g ethinyl estradiol for 23-25 days beginning on day 1 of the menstrual cycle. Following the 23-25-day period, an estrogen at a daily dosage equivalent to 5-15 μ g ethinyl estradiol is administered for 3-5 days. The total administration during each cycle is 28 days.

10 Preferred estrogens include, but are not limited to ethinyl estradiol; 17 β -estradiol; conjugated estrogens, USP; estrone or a salt thereof; and mestranol; with ethinyl estradiol being more preferred. When ethinyl estradiol is used as the estrogen during the first 23-25 days of the cycle, it is preferred that the daily dosage of ethinyl estradiol is 10-20 μ g, with 15 μ g being more preferred. When ethinyl estradiol is used
15 as the estrogen during the last 3-5 days of the cycle, it is preferred that the daily dosage of ethinyl estradiol is 5-15 μ g, with 15 μ g being more preferred. When 17 β -estradiol is used as the estrogen during the last 3-5 days of the cycle, it is preferred that the daily dosage of 17 β -estradiol is 1-3 μ g. Preferred salts of estrone include, but are not limited to the sodium and piperate salt. When conjugated estrogens, USP are used as the
20 estrogen, it is preferred that the daily dosage is 0.3-5 mg, with a daily dose of 1.25 mg conjugated estrogens, USP being equivalent to a daily dose of 15 μ g ethinyl estradiol.

It is preferred that the progestin/estrogen combination be administered for 24 days beginning on day 1 of the menstrual cycle, and following this 24-day period, it is preferred that the estrogen be administered for 4 days.

25 The following daily dosages of a combination of trimegestone and ethinyl estradiol are preferred for contraception when administered for 23-25 consecutive days beginning on the first day of menses, followed by the administration of ethinyl estradiol for 3-5 days. The total administration during each cycle is 28 days. It is preferred that the dose of ethinyl estradiol during the 3-5 day period be the same as the dose of ethinyl
30 estradiol that was administered during the 24 day period, or lower. Regimen B is most preferred.

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PREFERRED DAILY DOSAGES

5	Regimen	<u>First 23-25 Cycle Days</u>		<u>Last 3-5 Cycle Days</u>
		<u>Trimegestone</u>	<u>Ethinyl Estradiol</u>	<u>Ethinyl Estradiol</u>
	A	250 µg	15 µg	5-15 µg
	B	125 µg	15 µg	5-15 µg
	C	75 µg	15 µg	5-15 µg
	D	50 µg	15 µg	5-15 µg
10	E	40 µg	15 µg	5-15 µg

The following daily dosages of a combination of dienogest and ethinyl estradiol are preferred for contraception when administered for 23-25 consecutive days beginning on the first day of menses. Regimen B is most preferred.

15

PREFERRED DAILY DOSAGES

20	Regimen	<u>First 23-25 Cycle Days</u>		<u>Last 3-5 Cycle Days</u>
		<u>Dienogest</u>	<u>Ethinyl Estradiol</u>	<u>Ethinyl Estradiol</u>
	A	2 mg	15 µg	5-15 µg
	B	1 mg	15 µg	5-15 µg
	C	800 µg	15 µg	5-15 µg
	D	750 µg	15 µg	5-15 µg
	E	500 µg	15 µg	5-15 µg

25

The following daily dosages of a combination of drospirenone and ethinyl estradiol are preferred for contraception when administered for 23-25 consecutive days beginning on the first day of menses. Regimen C is most preferred.

PREFERRED DAILY DOSAGES

30	Regimen	<u>First 23-25 Cycle Days</u>		<u>Last 3-5 Cycle Days</u>
		<u>Drospirenone</u>	<u>Ethinyl Estradiol</u>	<u>Ethinyl Estradiol</u>
	A	3 mg	15 µg	5-15 µg
	B	2 mg	15 µg	5-15 µg
	C	1 mg	15 µg	5-15 µg
35	D	500 µg	15 µg	5-15 µg

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For administration during the first 23-25 days of the menstrual cycle, it is preferred that the combination progestin/estrogen contraceptive be administered in unit dosage form i.e., tablet or pill, with each unit providing the entire daily dosage. It is preferred that the progestin and estrogen are admixed together in the same dosage unit. Such dosage units can be prepared by conventional methodology that is well known to one skilled in the art. In each dosage unit, the contraceptively active progestin and estrogen are combined with excipients, vehicles, pharmaceutically acceptable carriers, and colorants. For example, the following illustrates an acceptable composition of a contraceptive progestin/estrogen combination of this invention.

EXAMPLE 1

Trimegestone, 125 μ g
Ethinyl estradiol, 15 μ g
Microcrystalline Cellulose
Lactose, NF, Spray Dried
Polacrillin Potassium, NF
Magnesium Stearate
Opadry Pink
Polyethylene Glycol, 1500, Flakes
Water, Purified, USP
Wax E (Pharma)

For administration during the last 3-5 days of the menstrual cycle, it is preferred that the estrogen be administered in unit dosage form i.e., tablet or pill, with each unit providing the entire daily dosage. Such dosage units can be prepared by conventional methodology that is well known to one skilled in the art. In each dosage unit, the estrogen is combined with excipients, vehicles, pharmaceutically acceptable carriers, and colorants. For example, the following illustrates an acceptable estrogen composition of this invention.

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EXAMPLE 2

5 Ethinyl estradiol, 15 µg
 Microcrystalline Cellulose
 Lactose, NF, Spray Dried
 Polacrillin Potassium, NF
 Magnesium Stearate
10 Opadry Pink
 Polyethylene Glycol, 1500, Flakes
 Water, Purified, USP
 Wax E (Pharma)

15

 This invention also provides a contraceptive kit adapted for daily oral
administration which comprises a total of 28 separate dosage units. In this kit, 23-25
dosage units each consisting of a combination of 40-500 µg trimegestone, 250 µg - 4
mg dienogest, or 250 µg - 4 mg drospirenone and an estrogen at a daily dosage
20 equivalent in estrogenic activity to 10-20 µg ethinyl estradiol. The remaining 3-5
dosage units contain an estrogen at a daily dosage equivalent in estrogenic activity to
5-15 µg ethinyl estradiol. The daily dosage arrangements are preferably arranged in a
blister pack or in a dial pack type tablet dispenser. Specific referred progestins and
estrogens and the specifically preferred dosages of each combination dosage unit are
25 described above.

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WHAT IS CLAIMED IS:

1. A method of contraception which comprises administering to a female of child bearing age a combination of a progestin at a daily dosage selected from the
5 group consisting of 40-500 μ g trimegestone, 250 μ g - 4 mg dienogest, and 250 μ g - 4 mg drospirenone, and an estrogen at a daily dosage equivalent in estrogenic
activity to 10-20 μ g ethinyl estradiol for 23-25 days beginning on day 1 of the menstrual cycle; wherein the same dosage of the progestin and estrogen combination is administered in each of the 23-25 days, followed by the
10 administration of an estrogen at a daily dosage equivalent in estrogenic activity to 5-15 μ g ethinyl estradiol for 3-5 days; wherein the same dosage of the estrogen is administered in each of the 3-5 days; such that the number of days of administration of the progestin and estrogen combination plus the number of days of administration of estrogen is equal to 28 per menstrual cycle.
- 15 2. The method according to claim 1, wherein the estrogen is selected from the group consisting of ethinyl estradiol; 17β -estradiol; conjugated estrogens, USP; estrone or a salt thereof; and mestranol.
- 20 3. The method according to claim 2, wherein the estrogen is ethinyl estradiol.
4. The method according to claim 3, wherein the progestin/estrogen combination is administered for 24 days per menstrual cycle beginning on day 1 of the menstrual cycle.
- 25 5. The method according to claim 4 wherein the daily dosage of ethinyl estradiol during the 24 day administration period is 15 μ g.
6. The method according to claim 5, wherein the progestin is trimegestone.
- 30 7. The method according to claim 6, wherein the daily dosage of trimegestone is 250 μ g.
8. The method according to claim 6, wherein the daily dosage of
35 trimegestone is 125 μ g.

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9. The method according to claim 6, wherein the daily dosage of
trimegestone is 75 μ g.
10. The method according to claim 6, wherein the daily dosage of
5 trimegestone is 50 μ g.
11. The method according to claim 6, wherein the daily dosage of
trimegestone is 40 μ g.
- 10 12. The method according to claim 5, wherein the progestin is dienogest.
13. The method according to claim 11, wherein the daily dosage of dienogest
is 2 mg.
- 15 14. The method according to claim 11, wherein the daily dosage of dienogest
is 1 mg.
15. The method according to claim 11, wherein the daily dosage of dienogest
is 800 μ g.
- 20 16. The method according to claim 11, wherein the daily dosage of dienogest
is 750 μ g.
17. The method according to claim 11, wherein the daily dosage of dienogest
25 is 500 μ g.
18. The method according to claim 5, wherein the progestin is drospirenone.
19. The method according to claim 18, wherein the daily dosage of
30 drospirenone is 3 mg.
20. The method according to claim 18, wherein the daily dosage of
drospirenone is 2 mg.
- 35 21. The method according to claim 18, wherein the daily dosage of
drospirenone is 1 mg.

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22. The method according to claim 18, wherein the daily dosage of drospirenone is 500 µg.

5 23. A contraceptive kit adapted for daily oral administration which comprises
28 separate dosage units, 23-25 separate dosage units, said dosage units each
containing a combination of a progestin at a dosage selected from the group
consisting of 40-500 µg trimegestone, 250 µg - 4 mg dienogest, and 250 µg - 4
10 mg drospirenone, and an estrogen at a dosage equivalent in estrogenic activity to
10-20 µg ethinyl estradiol, wherein each of the dosage units contains the same
dosage of progestin and estrogen; and 3-5 of said dosage units containing an
estrogen at a daily dosage equivalent in estrogenic activity to 5-15 µg ethinyl
estradiol, wherein each of the 3-5 dosage units contains the same dosage of
estrogen.

15

24. The contraceptive kit according to claim 23, wherein the estrogen is
selected from the group consisting of ethinyl estradiol; 17β-estradiol; conjugated
estrogens, USP; estrone or a salt thereof; and mestranol.

20 25. The contraceptive kit according to claim 24, wherein the estrogen is
ethinyl estradiol.

26. The contraceptive kit according to claim 25, wherein 24 of the 28 dosage
units contain the progestin and estrogen combination, and 4 of the dosage units
25 are progestin free.

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ANEXO 6

PCT

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US97/12795 (22) International Filing Date: 23 July 1997 (23.07.97) (30) Priority Data: 08/686,790 26 July 1996 (26.07.96) US (71) Applicant: AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Giralda Farms, Madison, NJ 07940-0874 (US). (72) Inventor: GAST, Michael, Jay; 230 Country Lane, Phoenixville, PA 19460 (US). (74) Agents: ALICE, Ronald, W.; American Home Products Corporation, Patent Law Dept. - 2B, One Campus Drive, Parsippany, NJ 07054 (US) et al.	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	

(54) Title: MONOPHASIC CONTRACEPTIVE METHOD AND KIT COMPRISING A COMBINATION OF A PROGESTIN AND ESTROGEN**(57) Abstract**

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

Novelad.

Drospirenona - Ethinylestradiol

MONOPHASIC CONTRACEPTIVE METHOD AND KIT COMPRISING A COMBINATION OF A
PROGESTIN AND ESTROGEN

BACKGROUND OF THE INVENTION

5 The vast majority of oral contraceptives consist of a combination of a progestin and estrogen that are administered concurrently for 21 days followed either by a 7 day pill free interval or by the administration of a placebo for 7 days in each 28 day cycle. The most important aspects of a successful oral contraceptive product are effective
10 contraception, good cycle control (absence of spotting and breakthrough bleeding and occurrence of withdrawal bleeding), and minimal side effects. Combination oral contraceptives have traditionally acted by suppression of gonadotropins. In addition, it appears that the progestin component is primarily responsible for contraceptive efficacy through inhibition of ovulation, and other peripheral effects which include changes in
15 the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation). The estrogenic component intensifies the anovulatory effect of the progestin, and is also important for maintaining cycle control.

 Since the introduction of oral contraceptives (OCs) over a quarter-century ago, research has been directed toward developing preparations that minimize the potential
20 for side effects while maintaining efficacy and normal menstrual patterns. The first-generation OCs contained more progestin and estrogen than was necessary to prevent conception. Adverse hemostatic and metabolic changes, clinical problems, and side effects were associated with these high-dose preparations. In 1978, the World Health Organization (WHO) recommended that the focus of OC research should be the
25 development of products containing the lowest possible dose levels of estrogen and progestin.

 The first reductions in steroid content in a combination pill were focused on estrogen because it, rather than progestin, was thought to be related to the most serious side effects. Reduction in progestin content followed, as evidence mounted that
30 lowering progestin intake might lower the risk of cardiovascular complications such as stroke and ischemic heart disease. [Kay CR, Am J Obstet Gynecol 142:762 (1982)]. However, this evidence was not as clear as that implicating estrogen in thromboembolic disorders. [Inman WHW, Br Med J 2:203 (1970); Stolley PD, Am J Epidemiol 102:197 (1975)]. The need for a balance between estrogens and progestins to minimize
35 adverse effects on carbohydrate metabolism and on lipid and lipoprotein levels was also recognized. [Bradley DD, N Engl J Med 299:17 (1978); Wynn V, Lancet 1:1045

(1979)]. Researchers then found that the synergistic action between progestin and estrogen in a balanced ratio successfully inhibited ovulation at low levels of both components.

5 Research into low-dose progestins was advanced significantly by the development of norgestrel (Ng) and levonorgestrel (LNg). Levonorgestrel is the biologically active moiety of racemic norgestrel. It is strongly progestational, has no inherent estrogenic activity, is antiestrogenic, and possesses good biologic activity. The contraceptive effects of levonorgestrel are manifested throughout the hypothalamic-pituitary-gonadal-target organ axis.

10 Ethinyl estradiol (EE) is the estrogen most frequently used in combination OCs. In attempts to fulfill the WHO objective, the dosage of EE in marketed OC formulations has been steadily reduced from that found in earlier OCs. Thromboembolic mortality decreased when the amount of synthetic estrogen in OC formulations was reduced from 100 µg to 50 µg. Subsequently, a significant reduction in fatal myocardial infarctions was reported for women using OCs with 30 µg of EE rather than 50 µg of EE. [Meade TW, Br Med J 280:1157 (1980)].

15 In keeping with the goal of reducing the total steroidal dosage, while maintaining contraceptive efficacy, good cycle control, and minimizing side effects, numerous regimens have been developed in which the progestin/estrogen combination is administered either as a fixed dosage combination (monophasic) or as biphasic or triphasic regimens in which the dosage of the combination is varied either once or twice throughout the menstrual cycle. In these regimens, the progestin/estrogen combination is typically administered for 21 days followed by either a 7-day pill free period or the administration of a non-contraceptive placebo (or iron supplement) for 7 days. In these regimens, 3-ketodesogestrel (3-KDSG), desogestrel (DSG), levonorgestrel (LNg), gestodene (GTD), norgestrel (NG), and norethindrone (NE) are typically used as the progestin while ethinyl estradiol (EE); 17β-estradiol, and mestranol are typically the estrogenic components. Other progestins less frequently used include drospirenone (DRSP) and dienogest (DGST).

30 An oral contraceptive product containing a combination of 3 mg DGST and 30 µg EE for 21-day administration per cycle is marketed in Germany.

Several examples of attempts at reducing the total steroidal dosage are provided below.

35 Spona (PCT Publication WO 95/17194) discloses contraceptive regimens which consist of the administration of a combination of a progestin (50 - 75 µg GTD, 75 - 125 µg LNg, 60 - 150 µg DSG, 60 - 150 µg 3-KDSG, 100 - 300 µg DRSP, 100 - 200 µg

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cyproterone acetate, 200 - 300 µg norgestimate, or >350 - 750 µg norethisterone) and an estrogen (15 - 20 µg EE or 2 - 6 mg 17β-estradiol) for 23-24 days per cycle.

5 Oettel (EP 628,312 A1) discloses combination contraceptive combinations containing the combination of three components: a biogenic estrogen (estradiol, estrone, or estriol), a synthetic estrogen (EE or mestranol), and a progestin (LNg, desogestrel, progesterone, norethisterone acetate, DGST, chlormadinone acetate, gestodene, or cyproterone acetate). In one embodiment, the combination is administered for 21 days followed by the administration of placebo (or pill free) or an estrogen on days 22-28 of the cycle.

10 Oettel (EP 696,454 A2) discloses a three phase contraceptive regimen in which the first phase consists of the administration for 3-4 days of a composition containing at least one biogenic estrogen; the second phase consists of the administration for 20-22 days of at least one biogenic estrogen and at least one progestin (progesterone, DGST, desogestrel, 3-KDSG, GTD, LNg, norgestimate, notethisterone, norethisterone acetate, 15 dehydrogestrone, chloromadinone acetate, cyproterone acetate, medroxyprogesterone acetate, or megestrol acetate); and the third phase consists of the administration for 3-4 days of a composition containing at least biogenic one estrogen.

Lachnit (PCT Publication WO 95/26730) discloses bridged regimens consisting of the administration of a combination of a progestin/estrogen combination (50 - 125 µg 20 LNg and 10 - 40 µg EE) for the first 23-24 days of the menstrual cycle followed by the administration of an estrogen (2 - 40 µg EE) for 4-10 days for a total administration of at least 28 days per cycle. The use of 100 - 300 µg drospirenone and 10 - 40 µg EE as the 23-24 day progestin/estrogen combination is disclosed. Lachnit also discloses a triphasic plus bridging regimen (4-9 days, 4-9 days, 9-13 days, and 28 days for the 25 three phases and estrogen phase, respectively) in which a combination of 50 µg LNg and 20 µg EE are administered in the first phase, a combination of 75 µg LNg and 25 µg EE are administered in the second phase, a combination of 100 µg LNg and 20 µg EE are administered in the third phase, and 10 µg EE is administered in the estrogen phase. Other progestins disclosed include GTD, DSG, 3-KDSG, DRSP, cyproterone 30 acetate, norgestimate, and norethisterone.

Upton (EP Patent Specification 253,607 B1) teaches the use of low dose progestin/estrogen combinations for combined hormone replacement therapy and contraception in climacteric women. Climacteric women are defined in Upton as pre-menopausal women around 40 years of age whose hormone levels are waning. The 35 climacteric woman still ovulates (albeit may have irregular ovulation), but she still

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experiences many of the symptoms of the hypoestrogenic menopausal woman, such as insomnia, hot flushes, and irritability. Upton teaches the administration of a 23-26 day monophasic regimen of progestin/estrogen followed by a pill free or placebo interval of 2-5 days; with 24 days of progestin/estrogen administration followed by a 4-day pill free or placebo administration being preferred. Upton teaches the use of a progestin selected from 25 - 100 μ g LNg, 10 - 70 μ g GTD, 25 - 100 μ g DSG, 25 - 100 μ g 3-KDSG, and 85 - 350 μ g NE used in combination with an estrogen selected from 500 - 2000 μ g 17 β -estradiol, 8 - 30 μ g EE, and 15 - 60 μ g mestranol. Based on relative potencies, Upton teaches that a dose of 75 μ g LNg is equivalent to 35 μ g of GTD, 75 μ g of 3-KDSG or DSG, and 250 μ g NE and that a dose of 1000 μ g of 17 β -estradiol is equivalent to a dose of 15 μ g EE and 30 μ g mestranol. Upton also teaches that NG may be substituted for LNg, but at twice the dose.

Sartoretto (Clinica e Terapeutica 3: 399 (1974)) discloses a monophasic contraceptive regimen consisting of the administration of a combination 100 μ g LNg and 20 μ g EE for 21 days.

Lachnit-Fixson (U.S. Patent 3,969,502) discloses biphasic progestin/estrogen combination regimens in which a combination of 50-125 μ g LNg and 25-35 μ g EE are administered for 10-12 days in the first phase and 100-350 μ g LNg and 30-50 μ g EE are administered for 10-12 days in the second phase. Placebo is administered for 5-7 days following the administration of the contraceptive steroid regimen.

Lachnit-Fixson (U.S. Patent 3,957,982) discloses triphasic 21-day progestin/estrogen regimens in which a combination of 40-90 μ g LNg and 20-50 μ g EE is administered for 4-6 days in the first phase, 50-125 μ g LNg and 30-50 μ g EE is administered for 4-6 days in the second phase, and 100-250 μ g LNg and 25-50 μ g EE is administered for 9-11 days in the third phase. It is preferred that the first, second, and third phases are 6, 5, and 10 days, respectively.

Bennick (U.S. Patent 5,418,228) discloses triphasic regimens which consist of the administration of a combination progestin/estrogen in a 6-8 day phase, a second 6-8 day phase, and a third 6-8 day phase, with it being preferred that the three contraceptive steroid phases be 7 days each. Bennick discloses that the first contraceptive steroid phase consists of a progestin at a daily dosage equivalent to 75 - 150 μ g DSG and an estrogen at a daily dosage equivalent to 20 - 25 μ g EE; the second contraceptive steroid phase consists of a progestin at a daily dosage equivalent to 75 - 125 μ g DSG and an estrogen at a daily dosage equivalent to 20 μ g EE; and the third contraceptive steroid phase consists of a progestin at a daily dosage equivalent to 75 - 100 μ g DSG and an estrogen at a daily dosage equivalent to 20 μ g EE. Placebo is administered for 7

days following the 21-day contraceptive steroid period. Bennick discloses that the progestin may be 3-KDSG, DSG, LNg, or GTD.

Bergink (U.S. Patent 5,262,408) discloses a 24 day triphasic combination regimen in which the first 7-9 day phase consists of the administration of a progestin at a daily dosage equivalent to 100 µg DSG and an estrogen at a daily dosage equivalent to 25 µg EE, the second 7-9 day phase consists of the administration of a progestin at a daily dosage equivalent to 125 µg DSG and an estrogen at a daily dosage equivalent to 20 µg EE, and the third 7-9 day phase consists of the administration of a progestin at a daily dosage equivalent to 50 µg DSG and an estrogen at a daily dosage equivalent to 20 µg EE. It is preferred that the three phases be 8 days each. Following the 24 day contraceptive steroid administration, a placebo may be administered for 4 days, the 4 day interval may be pill free, or a progestin at a dosage equivalent to 25-35 µg DSG may be administered.

Boissonneault (U.S. Patent 4,962,098) discloses triphasic progestin/estrogen combinations in which the amount of the estrogenic component is increased stepwise over the three phases. Contraceptive steroid combinations are taken for 4-7 days during the first phase (5 days being preferred); for 5-8 days during the second phase (7 days preferred); and for 7-12 days during the third phase (9 days being preferred). Following the administration of 21-days of the contraceptive steroid combination, placebo is taken for 7 days. For all three phases, 0.5-1.5 mg of norethindrone acetate is used in the progestin, with 1 mg being preferred. 10-30 µg EE is used in the first phase, 20-40 µg in the second, and 30-50 µg in the third phase.

Pasquale (U.S. Patent 4,921,843) discloses combination progestin/estrogen contraceptive regimens which contain 0.5 to 1 mg of progestin and an estrogen having a dose equivalent to 10-40 µg of EE. NE, LNg, D-17β-acetoxy-13β-ethyl-17α-ethinylgon-4-en-3-one oxime, and 19-nor-17-hydroxy progesterone ester are disclosed as progestins, with NE being preferred. Specifically disclosed regimens include a uniphasic regimen (2 days of placebo, 5 days of 20 µg EE, and 21 days of a combination of 500 µg NE and 35 µg EE); a uniphasic regimen (2 days of placebo, 5 days of 40 µg EE, and 21 days of a combination of 500 µg NE and 35 µg EE); and a triphasic regimen (2 days of placebo; 5 days of 20-40 µg EE; 7 days of a combination of 500 µg NE and 35 µg EE; 7 days of a combination of 750 µg NE and 35 µg EE; and 7 days of a combination of 1 mg NE and 35 µg EE).

Pasquale (U.S. Patent 4,628,051) discloses triphasic progestin/estrogen combination regimens in which contraceptive steroid is administered for 21 days. Contraceptive steroid combinations are taken for 5-8 days during the first phase (7 days

being preferred); for 7-11 days during the second phase (7 days preferred); and for 3-7 days during the third phase (7 days being preferred). In all three phases, an estrogen at a daily dosage equivalent to 20-50 μg EE is administered in combination with a progestin having a daily dosage equivalent to 65-750 μg NE in the first phase, 0.25-1.0 mg NE in the second phase, and 0.35-2.0 mg NE in the third phase. A specific triphasic regimen discloses the administration of 35 μg EE in each of the three 7-day phases in combination with 0.5 mg, 0.75 mg, and 1.0 mg in the first, second, and third phases, respectively. A second specific triphasic regimen discloses the administration of 35 μg EE in each of the three 7-day phases in combination with 50 μg , 75 μg , and 100 μg in the first, second, and third phases, respectively. A third specific triphasic regimen discloses the administration of 35 μg EE in each of the three 7-day phases in combination with 25 μg , 35 μg , and 50 μg in the first, second, and third phases, respectively.

Lachnit-Fixson (U.S. Patent 4,621,079) discloses triphasic 21-day progestin/estrogen combination regimens in which a combination of 40-70 μg GTD and 20-35 μg EE is administered for 4-6 days in the first phase; 50-100 μg GTD and 30-50 μg EE is administered for 4-6 days in the second phase; and 80-120 μg GTD and 20-50 μg EE is administered for 9-11 days in the third phase. Placebo is administered for 7 days following the 21-day contraceptive steroid regimen.

Pasquale (U.S. Patent 4,530,839) discloses triphasic 21-day progestin/estrogen combination regimens in which a dose of 20-50 μg EE is administered in all three phases in combination with a contraceptively effective daily dose of progestin in the first phase, 1.5-2 times that dose of progestin in the second phase, and 2-2.5 times the first phase dose of progestin in the third phase. Each of the three phases is 7 days long. A specific regimen discloses 20-50 μg EE in combination with 500 μg LNg, 750 μg LNg, and 1 mg LNg during each of the three 7-day phases, respectively.

Edgren (U.S. Patent 4,390,531) discloses triphasic 21-day progestin/estrogen combination regimens in which a dose of 20-40 μg EE (or another estrogen in an equivalent dosage) is administered in all three phases in combination with 0.3-0.8 mg NE (or another progestin in an equivalent dosage) for 5-8 days in the first phase, twice the dose of NE for 7-11 days in the second phase, and the dose of NE being the same as in the first phase for 3-7 days in the third phase. It is preferred that each of the three phases is 7 days. Placebo is administered for 6-8 days following administration of the contraceptive steroid combination. A specific regimen discloses a first phase of 7 days of 0.5 mg NE in combination with 35 μg EE, a second 7 day phase of 1.0 mg NE in

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combination with 35 µg EE, and a third 7 day phase of 0.5 mg NE in combination with 35 µg EE.

Moore (DE 4313926 A1) discloses bridged triphasic regimens consisting of the administration of a combination of 10 - 50 µg LNG and 5 - 20 µg EE from days 1-7 of the menstrual cycle; of 50 - 75 µg LNG and 5 - 20 µg EE from days 8-14 of the menstrual cycle; of 75 - 125 µg LNG and 5 - 20 µg EE from days 15-21 of the menstrual cycle; and 5 - 20 µg EE from days 22-28 of the menstrual cycle.

Erlich (German Patent DE 4,104,385 C1 and U.S. Patent 5,280,023) discloses sequential contraceptive regimens consisting of the administration of an estrogen which effects a disturbance of follicle stimulation, followed by the administration of a combination of a progestin/estrogen in a dose at least adequate to inhibit ovulation. The regimen is administered for a total of 28 days per cycle. It is preferred that the estrogen is administered for 5-14 days per cycle and the progestin/estrogen combination is administered for 23-14 days per cycle, so that the total administration is for 28 days per cycle. Specific regimens include (a) 4 mg estradiol for 7 days followed by 21 days of the combination of 1 mg norethisterone acetate and 4 mg estradiol; (b) 2 mg estradiol valerate for 7 days followed by 21 days of the combination of 2 mg chlormadinone acetate and 4 mg estradiol valerate; and (c) 20 µg EE followed by 18 days of the combination of 150 µg LNG and 20 µg EE. Regimen (c) in Erlich provides a total steroidal load of 2.7 mg of LNG and 560 µg EE per 28 day cycle.

DESCRIPTION OF THE INVENTION

This invention provides a monophasic combination progestin/estrogen oral contraceptive regimen for females of child-bearing age that provides effective contraception, good cycle control, and minimal side effects while greatly reducing the total contraceptive steroid administered (particularly the estrogenic component) per 28-day cycle. To achieve the substantial reduction in the total contraceptive steroid administered per cycle while maintaining good cycle control, the low dose progestin/estrogen combination is administered for 23-25 days per cycle. Administration of the contraceptive progestin/estrogen combination is begun on the first day of menses (day 1), and continued for 23-25 consecutive days. Following the 23-25-day administration period, a non-contraceptive placebo (devoid of progestins and estrogens) can be provided for 3-5 days to aid in compliance with the desired

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contraceptive regimen. Alternatively, the 3-5-day interval can be pill free. The total cycle length is 28 days.

More particularly, this invention provides a method of contraception which comprises administering to a female of child bearing age a combination of 40-500 μ g trimegestone, 250 μ g - 4 mg dienogest, or 250 μ g - 4 mg drospirenone, and an estrogen at a daily dosage equivalent in estrogenic activity to 10-20 μ g ethinyl estradiol for 23-25 days beginning on day 1 of the menstrual cycle. Following the 23-25-day administration period, a non-contraceptive placebo (devoid of progestins and estrogens) can be provided for 3-5 days to aid in compliance with the desired contraceptive regimen. Alternatively, the 3-5-day interval can be pill free. The total cycle length is 28 days.

Preferred estrogens include, but are not limited to ethinyl estradiol; 17 β -estradiol; conjugated estrogens, USP; estrone or a salt thereof; and mestranol; with ethinyl estradiol being more preferred. When ethinyl estradiol is used as the estrogen, it is preferred that the daily dosage of ethinyl estradiol is 10-20 μ g, with 15 μ g being more preferred. Preferred salts of estrone include, but are not limited to the sodium and piperate salt. When conjugated estrogens, USP are used as the estrogen, it is preferred that the daily dosage is 0.3-5 mg, with a daily dose of 1.25 mg conjugated estrogens, USP being equivalent to a daily dose of 15 μ g ethinyl estradiol.

Following the 23-25-day period, a non-contraceptive placebo, which may contain an iron supplement, such as 75 mg of ferrous fumarate, may be administered for 4 days (through day 28 of the menstrual cycle) or the 4 days following administration of the contraceptive combination may be pill free.

It is preferred that the progestin/estrogen combination be administered for 24 days beginning on day 1 of the menstrual cycle.

The following daily dosages of a combination of trimegestone and ethinyl estradiol are preferred for contraception when administered for 23-25 consecutive days beginning on the first day of menses. Regimen B is most preferred.

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PREFERRED DAILY DOSAGES

Regimen	Trimegestone	Ethinyl Estradiol
A	250 μ g	15 μ g
B	125 μ g	15 μ g
C	75 μ g	15 μ g
D	50 μ g	15 μ g
E	40 μ g	15 μ g

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The following daily dosages of a combination of dienogest and ethinyl estradiol are preferred for contraception when administered for 23-25 consecutive days beginning on the first day of menses. Regimen B is most preferred.

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PREFERRED DAILY DOSAGES

Regimen	Dienogest	Ethinyl Estradiol
A	2 mg	15 µg
B	1 mg	15 µg
C	800 µg	15 µg
D	750 µg	15 µg
E	500 µg	15 µg

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The following daily dosages of a combination of drospirenone and ethinyl estradiol are preferred for contraception when administered for 23-25 consecutive days beginning on the first day of menses. Regimen C is most preferred.

PREFERRED DAILY DOSAGES

Regimen	Drospirenone	Ethinyl Estradiol
A	3 mg	15 µg
B	2 mg	15 µg
C	1 mg	15 µg
D	500 µg	15 µg

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It is preferred that the combination progestin/estrogen contraceptive be administered in unit dosage form i.e., tablet or pill, with each unit providing the entire daily dosage. It is preferred that the progestin and estrogen are admixed together in the same dosage unit. Such dosage units can be prepared by conventional methodology that is well known to one skilled in the art. In each dosage unit, the contraceptively active progestin and estrogen are combined with excipients, vehicles, pharmaceutically acceptable carriers, and colorants. For example, the following illustrates an acceptable composition of a contraceptive progestin/estrogen combination of this invention.

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EXAMPLE 1

5 Trimegestone, 125 μ g
Ethinyl estradiol, 15 μ g
Microcrystalline Cellulose
Lactose, NF, Spray Dried
Polacrillin Potassium, NF
Magnesium Stearate
Opadry Pink
10 Polyethylene Glycol, 1500, Flakes
Water, Purified, USP
Wax E (Pharma)

15 This invention also provides a contraceptive kit adapted for daily oral administration which comprises 23-25 separate dosage units, said dosage units each consisting of a combination of 40-500 μ g trimegestone, 250 μ g - 4 mg dienogest, or 250 μ g - 4 mg mg drospirenone, and an estrogen at a daily dosage equivalent in estrogenic activity to 10-20 μ g ethinyl estradiol. In another embodiment, the
20 contraceptive kit contains 28 daily dosage units with 3-5 being a non-contraceptive placebo, that may contain an iron supplement, such as 75 mg ferrous fumarate. The daily dosage arrangements are preferably arranged in a blister pack or in a dial pack type tablet dispenser.

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WHAT IS CLAIMED IS:

1. A method of contraception which comprises administering to a female of child bearing age a combination of a progestin at a daily dosage selected from the group consisting of 40-500 μg trimegestone, 250 μg - 4 mg dienogest, and 250 μg - 4 mg drospirenone, and an estrogen at a daily dosage equivalent in estrogenic activity to 10-20 μg ethinyl estradiol for 23-25 days beginning on day 1 of the menstrual cycle, and wherein the same dosage of the progestin and estrogen combination is administered in each of the 23-25 days.
2. The method according to claim 1, wherein the estrogen is selected from the group consisting of ethinyl estradiol; 17 β -estradiol; conjugated estrogens, USP; estrone or a salt thereof; and mestranol.
3. The method according to claim 2, wherein the estrogen is ethinyl estradiol.
4. The method according to claim 3, wherein the progestin/estrogen combination is administered for 24 days per menstrual cycle beginning on day 1 of the menstrual cycle.
5. The method according to claim 4 wherein the daily dosage of ethinyl estradiol is 15 μg .
6. The method according to claim 5, wherein the progestin is trimegestone.
7. The method according to claim 6, wherein the daily dosage of trimegestone is 250 μg .
8. The method according to claim 6, wherein the daily dosage of trimegestone is 125 μg .
9. The method according to claim 6, wherein the daily dosage of trimegestone is 75 μg .
10. The method according to claim 6, wherein the daily dosage of trimegestone is 50 μg .

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11. The method according to claim 6, wherein the daily dosage of trimegestone is 40 μ g.
- 5 12. The method according to claim 5, wherein the progestin is dienogest.
13. The method according to claim 11, wherein the daily dosage of dienogest is 2 mg.
- 10 14. The method according to claim 11, wherein the daily dosage of dienogest is 1 mg.
15. The method according to claim 11, wherein the daily dosage of dienogest is 800 μ g.
- 15 16. The method according to claim 11, wherein the daily dosage of dienogest is 750 μ g.
17. The method according to claim 11, wherein the daily dosage of dienogest is 500 μ g.
- 20 18. The method according to claim 5, wherein the progestin is drospirenone.
19. The method according to claim 18, wherein the daily dosage of drospirenone is 3 mg.
- 25 20. The method according to claim 18, wherein the daily dosage of drospirenone is 2 mg.
21. The method according to claim 18, wherein the daily dosage of drospirenone is 1 mg.
- 30 22. The method according to claim 18, wherein the daily dosage of drospirenone is 500 μ g.

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23. The method according to claim 1, which further comprises administering a non-contraceptive placebo for 3-5 consecutive days beginning on the day immediately following the last day of administration of the progestin/estrogen combination, such that the total days of administration of the progestin/estrogen combination plus the non-contraceptive placebo equals 28 days.

24. The method according to claim 23 in which the non-contraceptive placebo contains an iron supplement.

25. A contraceptive kit adapted for oral administration which comprises 23-25 separate dosage units, said dosage units each containing a combination of a progestin at a dosage selected from the group consisting of 40-500 μg trimegestone, 250 μg - 4 mg dienogest, and 250 μg - 4 mg drospirenone, and an estrogen at a dosage equivalent in estrogenic activity to 10-20 μg ethinyl estradiol, wherein each of the dosage units contains the same dosage of progestin and estrogen.

26. The contraceptive kit according to claim 25, wherein the estrogen is selected from the group consisting of ethinyl estradiol; 17 β -estradiol; conjugated estrogens, USP; estrone or a salt thereof; and mestranol.

27. The contraceptive kit according to claim 26, wherein the estrogen is ethinyl estradiol.

28. The contraceptive kit according to claim 27 in which the number of dosage units is 24.

29. A contraceptive kit adapted for oral administration which comprises 28 dosage separate units, 23-25 of said dosage units each containing each containing a combination of a progestin at a dosage selected from the group consisting of 40-500 μg trimegestone, 250 μg - 4 mg dienogest, and 250 μg mg drospirenone, and an estrogen at a dosage equivalent in estrogenic activity to 10-20 μg ethinyl estradiol, wherein each of the dosage units contains the same dosage of progestin and estrogen; and 3-5 of said dosage units each containing a non-contraceptive placebo; wherein each of the 23-25 dosage units contains the same dosage of progestin and estrogen.

ANEXO 7



US005583129A

United States Patent [19]**Spona et al.**[11] **Patent Number:** **5,583,129**[45] **Date of Patent:** **Dec. 10, 1996**[54] **COMPOSITION FOR CONTRACEPTION**

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[21] Appl. No.: **268,996**[22] Filed: **Jun. 30, 1994**[30] **Foreign Application Priority Data**

Dec. 22, 1993 [DE] Germany 43 44 462.8

[51] **Int. Cl.⁶** **A61K 31/56**; A61K 31/57;
A61K 31/585

[52] **U.S. Cl.** **514/178**; 514/173; 514/182

[58] **Field of Search** 514/178, 182,
514/173

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Primary Examiner—Phyllis G. Spivack
Attorney, Agent, or Firm—Millen, White, Zelano, & Branigan, P.C.

[57] **ABSTRACT**

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

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

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

8 Claims, 1 Drawing Sheet

Novedad

Drospirenona - Ethinylestradiol

AREA WITH THE E2 LEVEL

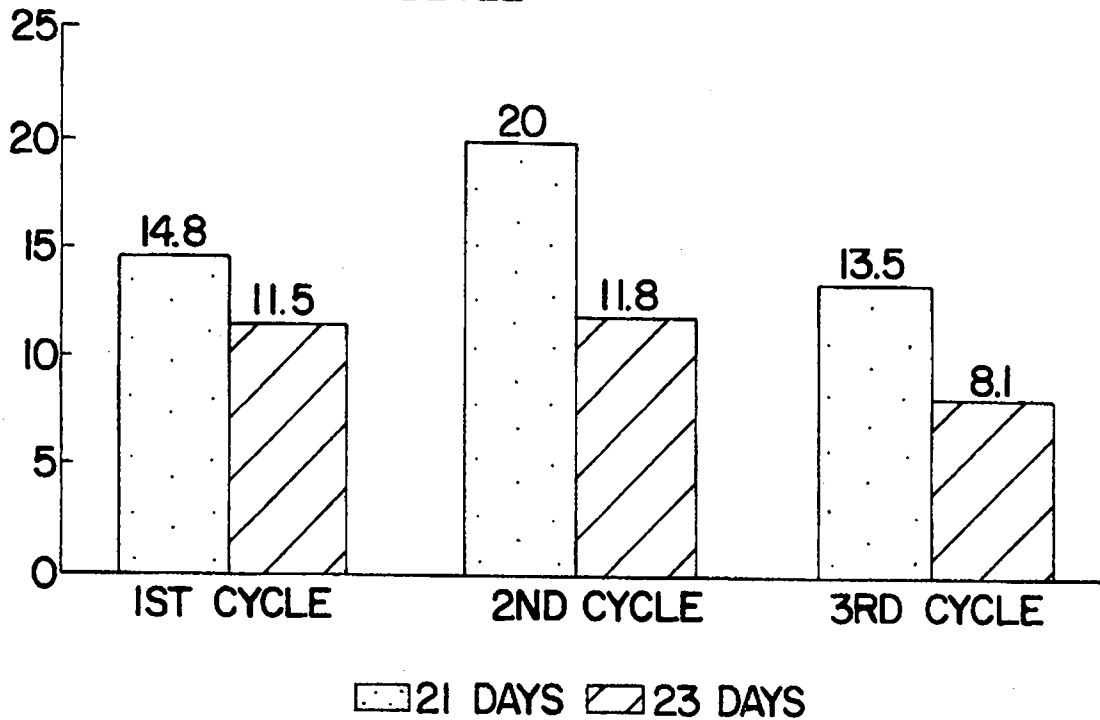


FIG. 1

% OF FEMALES WITH FOLLICULAR MATURATION

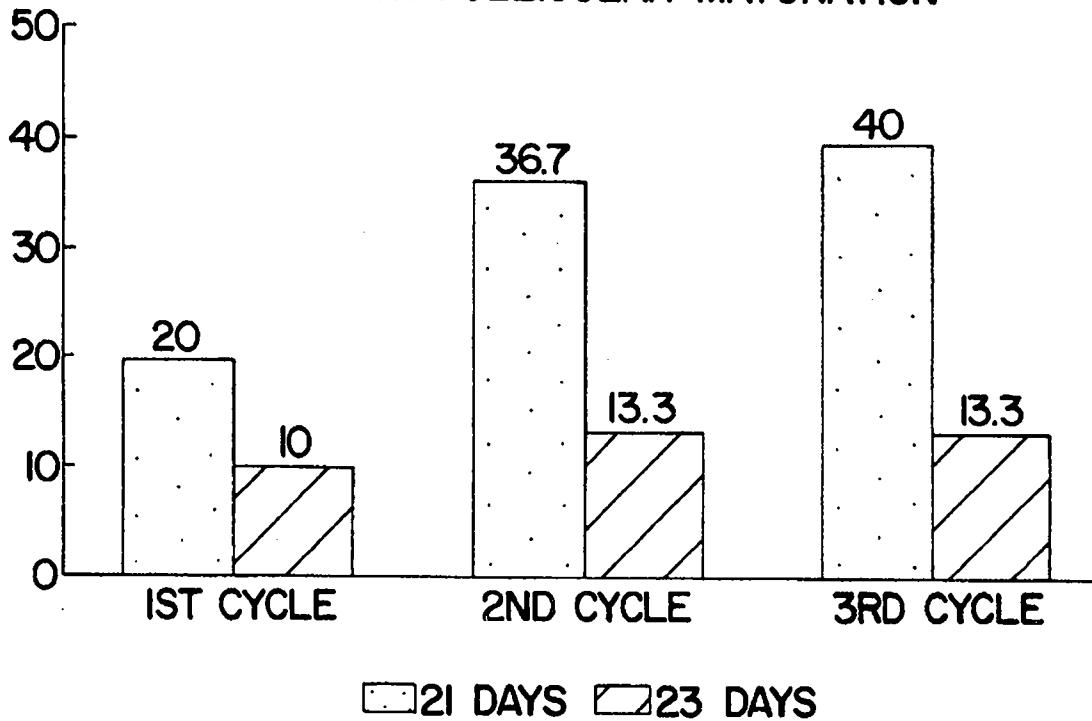


FIG. 2

COMPOSITION FOR CONTRACEPTION

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 Dis-

ease, 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, VIIIth 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 requirements 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 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.

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), e.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.

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.

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, in 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).

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 μ -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).

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.

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 μ g 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 17β -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 μ g 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 μ g 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, Femovan® (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 17β -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]; H. Kuhl in Gynäkologe" [Gynecologist] 25: 231-240 (1992).

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1: Area with the 17β -estradiol level in groups of 30 females, who are treated with an oral contraceptive (75 μ g of gestodene +20 μ g 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 μ g of gestodene +20 μ g of ethinylestradiol).

We claim:

1. A method of inducing contraception in a female of reproductive age who has not yet reached premenopause, comprising administering to said female a composition comprising an estrogen selected from

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

wherein the composition is administered for 23 or 24 days, beginning on day one of the menstrual cycle, followed by 5 or 4 pill-free or sugar pill days, during a total of 28 days in the administration cycle.

2. A method according to claim 1, whereby the estrogen is ethinylestradiol.

3. A method according to claim 1, whereby the estrogen is 17β -estradiol.

4. A method according to claim 1, whereby the gestagen is gestodene.

5. A method according to claim 1, whereby the gestagen is levonorgestrel.

6. A method according to claim 1, whereby the gestagen is cyproterone acetate or drospirenone.

7. A method according to claim 1, whereby the composition comprises an estrogen selected from

- >2.0 to 6.0 mg of 17β -estradiol and
- 0.020 mg of ethinylestradiol;

and a gestagen selected from

- >0.06 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.

8. A method according to claim 1, whereby the estrogen is present in a dose of 20 μ g of ethinylestradiol or an equivalent dose of 17β -estradiol and the gestagen is present in a dose of 75 μ g of gestodene or an equivalent dose of levonorgestrel, cyproterone acetate or drospirenone.

* * * * *

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(54) Title: PHARMACEUTICAL COMBINED PREPARATION, KIT AND METHOD FOR HORMONAL CONTRACEPTION

(54) Bezeichnung: PHARMAZEUTISCHES KOMBINATIONSPRÄPARAT, KIT UND METHODE ZUR HORMONALEN KONTRAZEPTION

(57) Abstract

Novedad: 1) Efinilenfradiol- Drospirenona
2) Efinilenfradiol

The invention concerns a two-stage pharmaceutical combined preparation for hormonal contraception containing at least 30 daily doses. The hormonal active substance in the first stage is a combination of an oestrogen preparation and a gestagen preparation in single-stage form in a quantity at least sufficient to inhibit ovulation. In the second stage, the hormonal active substance is an oestrogen preparation only. The first stage comprises not less than 25 and not more than 77 daily discrete or continuous doses and the second stage comprises 5, 6 or 7 daily discrete or continuous doses, the total number of daily units being equal to the total number of days of the desired cycle, i.e. at least thirty and not more than eighty four. This combined preparation can be made available in, for example, monthly packaging and is used for controlling female fertility. It reduces to a minimum the oestrogen content in each individual dose and also has a low overall hormone content for the dosing cycle, while ensuring a high contraceptive reliability, low incidence of follicle development, excellent cycle control and reliable prevention of intercycle menstrual bleeding and unwanted side effects.

(57) Zusammenfassung

Die vorliegende Erfindung beschreibt ein zweistufiges pharmazeutisches Kombinationspräparat zur hormonalen Kontrazeption enthaltend mindestens 30 tägliche Dosierungseinheiten, welches in seiner ersten Stufe als hormonellen Wirkstoff in Kombination ein Estrogen- und in mindestens zur Ovulationshemmung ausreichender Dosierung ein Gestagenpräparat in einstufiger Ausbildung und in der zweiten Stufe als hormonellen Wirkstoff lediglich ein Estrogenpräparat enthält, wobei die erste Stufe mindestens 25 und maximal 77 diskrete tägliche oder kontinuierliche Dosierungseinheiten und die zweite Stufe 5, 6 oder 7 tägliche diskrete oder kontinuierliche Dosierungseinheiten umfaßt und die Gesamtzahl der Tageseinheiten gleich der Gesamtzahl der Tage des gewünschten, mindestens 30 und maximal 84 Tage langen, Zyklus ist. Dieses beispielsweise als Monatspackung vorliegende Kombinationspräparat, das zur weiblichen Fertilitätskontrolle dient, gestattet einen möglichst niedrigen Estrogengehalt in jeder einzelnen Dosierungseinheit und weist auch einen niedrigen Gesamthormongehalt pro Verabreichungszyklus auf, bei hoher kontrazeptiver Sicherheit, geringer Inzidenz an Follikelentwicklung, einwandfreier Zykluskontrolle unter zuverlässiger Vermeidung von Zwischenblutungen sowie unerwünschter Nebenwirkungen.

Pharmazeutisches Kombinationspräparat, Kit und Methode zur hormonalen Kontrazeption

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Beschreibung

- Die vorliegende Erfindung betrifft ein zweistufiges pharmazeutisches
10 Kombinationspräparat zur hormonalen Kontrazeption enthaltend mindestens 30
tägliche Dosierungseinheiten, welches in seiner ersten Stufe als hormonellen
Wirkstoff in Kombination ein Estrogen- und in mindestens zur Ovulationshemmung
ausreichender Dosierung ein Gestagenpräparat in einstufiger Ausbildung und in der
zweiten Stufe als hormonellen Wirkstoff lediglich ein Estrogenpräparat enthält, wobei
15 die erste Stufe mindestens 25 und maximal 77 diskrete tägliche oder kontinuierliche
Dosierungseinheiten und die zweite Stufe 5, 6 oder 7 tägliche diskrete oder
kontinuierliche Dosierungseinheiten umfaßt und die Gesamtzahl der Tageseinheiten
gleich der Gesamtzahl der Tage des gewünschten, mindestens 30 und maximal 84
Tage langen, Zyklus ist,
20 sowie eine entsprechende, dieses Kombinationspräparat enthaltende Packung
(kontrazeptionelles Kit) und
eine kontrazeptive Methode, die sich des vorstehenden Kontrazeptionspräparates
bedient.
- 25 Orale Kontrazeptiva in Form von Kombinationspräparaten sind als sogenannte
Einphasenpräparate seit 1960 bekannt. Diese Präparate bestehen aus 21
wirkstoffhaltigen Dosierungseinheiten und 7 wirkstofffreien Tabletten oder Dragees.
Die tägliche Dosierungseinheit ist aus einem Estrogen und Gestagen
zusammengesetzt. In Einphasenpräparaten ist die täglich zu verabreichende Dosis der
30 aktiven Stoffe in jeder Dosierungseinheit gleich hoch. Wenn die täglich zu
verabreichende Dosis der aktiven Bestandteile in den einzelnen Dosierungseinheiten
in einzelnen Abschnitten über den Verabreichungszyklus unterschiedlich ist, handelt
es sich um sogenannte Mehrphasenpräparate. Als besonders namhafter Vertreter sei
Triquilar® genannt
35 (DE-A 23 65 103).

Durch die Entwicklung neuer, wirksamerer Gestagene als die in den ersten oralen
Kontrazeptiva enthaltenen, konnte die tägliche Gestagendosierung kontinuierlich
verringert werden. Auch die tägliche Estrogendosierung konnte gesenkt werden,

obwohl als Estrogen in hormonalen Kontrazeptiva nach wie vor meist Ethinylestradiol enthalten ist.

Bei der Entwicklung neuer, verbesserter oraler Kontrazeptiva standen (und stehen) folgende drei Gesichtspunkte im Vordergrund:

5 Es soll

- (1) die kontrazeptive Sicherheit,
 - (2) eine gute Zykluskontrolle, d.h. geringe Inzidenz an Zwischenblutungen und
 - (3) ein Minimum an unerwünschten Nebenwirkungen
- gewährleistet sein.

- 10 Die kontrazeptive Sicherheit wird vor allem durch die Gestagenkomponente bewirkt. Deren tägliche Dosierungsmenge entspricht jeweils mindestens der Grenzdosis, die für das betreffende Gestagen zur Ovulationshemmung als erforderlich angesehen wird. Das in Kombinationspräparaten als Estrogen meistens verwendete Ethinylestradiol soll den ovulationshemmenden Effekt des Gestagens erhöhen und vor allem die
- 15 Zyklusstabilität gewährleisten. Die tägliche Dosis bei alleiniger Verabreichung des Ethinylestradiols, die für eine Hemmung der Ovulation verwendet werden muss, beträgt 100 µg.

- Kombinationspräparate mit der jüngsten Generation von Gestagenen sind z.B. die
- 20 Einphasenpräparate Femovan (DE-PS 2546062) oder Marvelon (DE-OS 2361120). Als Mehrphasenpräparat, dessen Dosierungseinheiten ein Gestagen der jüngsten Generation, nämlich Gestoden, enthalten, ist beispielsweise Milvane® zu nennen (EP- 0 148 724). Bei diesen Dreiphasenpräparaten werden in der ersten Phase zumeist 4-6 Dragees verabreicht, in der jedes Dragee eine Estrogenmenge in geringer
- 25 Dosis und ein Gestagen in geringer Dosis enthält. In der zweiten Phase von 4-6 Dragees enthält jede Dosierungseinheit ein Estrogen mit gleicher oder gering angehobener, maximal bis auf das 2 fache gesteigerte Dosis und ein Gestagen mit gleicher oder gering angehobener, maximal auf das 1.5 fach gesteigerte Dosis. In einer dritten Phase von 9-11 Einheiten enthält jedes Dragee ein Estrogen mit gleicher
- 30 oder wieder gesenkter, maximal auf den Ausgangswert erniedrigter Dosis und ein Gestagen mit weiter angehobener, maximal auf das 3 fache des Ausgangswertes gesteigerter Dosis. Daran schliessen sich 7 pillenfreie Tage an.
- Neuerdings sind auch mehrphasische Kombinationspräparate vorgeschlagen worden, die eine verlängerte, d.h. bis zu 24tägige Einnahme wirkstoffhaltiger
- 35 Dosierungseinheiten im 28tägigen Zyklus vorsehen können. Dabei steigt die tägliche Gestagen-Dosierungsmenge von der ersten über die zweite bis zur dritten Phase entweder an (EP-A 0 491 415) oder sie nimmt ab (EP-A 0 491 438). Zur

Vervollständigung des 28 Tage langen Zyklus schließen sich im ersten Fall 4 Blindpillentage, 4 Placebos oder aber 4 ausschließlich gestagenhaltige Dosierungseinheiten oder im zweiten Fall 4 bis 7 Blindpillentage oder 4 bis 7 Placebos an.

5

Die Entwicklung neuer oraler Kontrazeptiva mit verringerter täglicher Hormondosis hatte zum Ziel, die in epidemiologischen Studien beschriebenen Nebenwirkungen zu minimieren. Neuere epidemiologische Daten weisen auf einen solchen Trend zur besseren Verträglichkeit niedriger dosierter Präparate hinsichtlich kardiovaskulärer Nebenwirkungen hin [Thorogood M, Oral Contraceptives and Cardiovascular Disease: An Epidemiologic Overview; Pharmacoepidemiology and Drug Safety, Vol 2: 3-16 (1993); 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); Lidegaard O, Oral contraception and risk of a cerebral thromboembolic attack: results of a case-control study; BMJ Vol 306, 956-63 (1993); Vessey M, Mant D, Smith A, Yeates D., Oral contraceptives and venous thromboembolism: findings in a large prospective study; BMJ, Vol 292, (1986); Mishell D R, Oral Contraception: Past, Present, and Future Perspectives; Int J Fertil, 36 Suppl., 7 - 18 (1991)].

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Ein Zusammenhang zwischen der Höhe der täglichen Estrogendosis und der Häufigkeit kardiovaskulärer Komplikationen wird angenommen.

Das Präparat mit der zur Zeit niedrigst dosierten Estrogenmenge ist als Mercilon® im Handel und enthält 20µg Ethinylestradiol in Kombination mit 150µg Desogestrel in jeder täglichen Dosierungseinheit über 21 Tage mit einem sich anschließenden 7 tägigen pillenfreien Intervall. Die Zykluskontrolle dieses Präparates ist im Vergleich zu Präparaten mit höherer Estrogendosis erwartungsgemäß etwas schlechter. Ein weiteres, klinisch bedeutsames Problem stellt die in mehreren Studien übereinstimmend gemachte Beobachtung einer geringeren ovariellen Suppression des 20µg Ethinylestradiol enthaltenden Präparates dar. Es kommt offensichtlich unter dieser sehr niedrigen Estrogendosis bei vielen Frauen zur Heranreife von Follikeln, die mit Ultraschalluntersuchungen bzw. Hormonuntersuchungen nachgewiesen werden konnten [Lunell N O, Carlström K, Zador G, Ovulation inhibition with a combined oral contraceptive containing 20 µg ethinylestradiol and 250 µg levonorgestrel; Acta Obstet Gynecol Scand Suppl. 88: 17-21 (1979); Mall-Haefeli M, Werner-Zodrow I, Huber P R, Klinische Erfahrungen mit Mercilon und Marvelon

unter besonderer Berücksichtigung der Ovar-Funktion; Geburtsh. und Frauenheilk. 51, 35-38, Georg Thieme Verlag, Stuttgart-New York (1991); Strobel E, Behandlung mit oralen Kontrazeptiva; Fortschr. Med. 110 Jg. Nr. 20 (1992); Letter to Editor, Contraception 45: 519-521 (1992); Teichmann A T, Brill K, Can Dose Reduction of
5 Ethinylestradiol in OCs jeopardize Ovarian Suppression and Cycle Control? Abstract Book, VIIIth World Congress on Human Reproduction, Bali, Indonesia (1993)].

Bis vor kurzem wurde eine mehrtägige Unterbrechung der Einnahme wirkstoffhaltiger
Dragees für notwendig gehalten, um eine Entzugsblutung auszulösen und eine
10 ausreichende Zykluskontrolle zu gewährleisten.

Andere Präparate wurden beschrieben, die einen estrogenen und gestagenen Wirkstoff enthalten und die im allgemeinen über 21 Tage in gleichbleibenden Mengen in jeder einzelnen Dosierungseinheit verabreicht werden, bei denen der Einnahme dieser
15 einen estrogenen und gestagenen Wirkstoff enthaltenden Dosierungseinheiten die Einnahme ausschließlich Estrogen-haltiger Dosierungseinheiten (Ijzerman, US-A 3,502,772; Pasquale, US-A 4,921,843; Kuhl et al., EP-A 0 499 348) vorausgeht. Bei diesen Präparaten wird bei Einnahmebeginn entweder bereits am ersten Zyklustag (Kuhl) oder frühestens am zweiten Zyklustag (Pasquale) mit der Einnahme von
20 Dosierungseinheiten begonnen, die nur einen estrogenen Wirkstoff enthalten, und zwar in einer Dosierung, die unter der ovulationshemmenden Dosis der estrogenen Komponente liegt, wodurch es, insbesondere im ersten Einnahmezyklus, zu Follikelentwicklungen kommen kann. Follikelentwicklungen werden für Durchbruchovulationen verantwortlich gemacht (Chowdhury et al., "Escape"
25 ovulation in women due to the missing of low dose combination oral contraceptive pills, Contraception, 22: 241-247, 1980; Molloy B.G. et al., "Missed pill" conception: fact or fiction? Brit.Med.J. 290, 1474-1475, 1985). Der kontrazeptive Schutz ist dadurch in Frage gestellt. Das Risiko einer Schwangerschaft ist daher insbesondere bei Einnahmefehlern unter den 20µg-Ethinylestradiol Präparaten hoch.

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Die DE-OS 43 13 926 ein mindestens vierphasiges pharmazeutisches Präparat zur Kontrazeption aus einer fixen oder sequentiellen, mindestens dreiphasigen Kombination von Ethinylestradiol oder Mestranol oder einem anderen synthetischen Estrogen sowie einem Gestagen und einem mindestens in der vierten Phase des
35 Zyklus zu applizierenden Estrogenpräparat, das Ethinylestradiol oder Mestranol und/oder ein anderes synthetisches und/oder körpereigenes Estrogen enthält. Dieses Präparat ist über den gesamten Zyklus der Frau zu verabreichen und ist auf eine 28tägige Verabreichung beschränkt.

Allen bisher am Markt befindlichen Präparaten zur hormonalen Kontrazeption ist gemein, daß deren jeweilige Verpackungseinheit auf einen 28-tägigen Einnahmezyklus ausgerichtet ist (4-Wochenrhythmus). Für einen einjährigen, d.h. 12-monatigen, Verhütungszeitraum ist also die Einnahme des Inhalts von 13
5 Verpackungseinheiten erforderlich.

Es ist allerdings bereits seit langer Zeit bekannt, daß sich der Eintritt der Menstruation unter der Einnahme eines oralen Kontrazeptivums durch kontinuierliche tägliche Einnahme sowohl estrogen- als insbesondere gestagenhaltiger
10 Dosierungseinheiten bis zur Beendigung der Einnahme der gestagenhaltigen Dosierungseinheiten hinausschieben läßt [Hamerlynck J. V. Th. H. et al., Contraception 35,3: 199-205 (1987); Luodon N. B., IPPF Med Bull 13,1: 2-3 (1979); Luodon N. B. et al., Brit Med J 60085: 487-490 (1977/2)]. Nach dem Absetzen der gestagenhaltigen Dosierungseinheiten tritt eine Entzugsblutung auf. Das
15 ovulationshemmende Mittel gemäß der EP-A 0 499 348 ist zwar nicht auf einen gewünschten Einnahmezyklus von 28 Tagen beschränkt, jedoch bleibt dort die Anzahl der sowohl estrogen- als auch gestagenhaltigen Hormontageseinheiten auf eine Obergrenze von 23 Tageseinheiten beschränkt.

20 Die Aufgabe der vorliegenden Erfindung ist es, ein Kombinationspräparat mit möglichst niedrigem Estrogengehalt in jeder einzelnen Dosierungseinheit aber auch mit einem niedrigen Gesamthormongehalt pro Verabreichungszyklus zur Verfügung zu stellen, wobei bei hoher kontrazeptiver Sicherheit bereits auch im ersten Einnahmezyklus eine möglichst geringe Inzidenz an Follikelentwicklung, eine
25 einwandfreie Zykluskontrolle unter zuverlässiger Vermeidung von Zwischenblutungen wie Durchbruchblutungen und "spottings" erreicht und unerwünschte Nebenwirkungen vermieden werden sollen.

Diese Aufgabe wird durch die Bereitstellung des eingangs beschriebenen
30 zweistufigen Kombinationspräparates sowie eine entsprechende, dieses Kombinationspräparat enthaltende Packung (kontrazeptionelles Kit) und eine kontrazeptive Methode, die sich des beschriebenen Kontrazeptionspräparates bedient, gelöst.

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Bevorzugte Ausführungsformen vorliegender Erfindung betreffen ein pharmazeutisches Kombinationspräparat der eingangs angegebenen Art, bei dem

- 5 - die erste Stufe 25 oder 26 tägliche Dosierungseinheiten umfaßt,
 - die erste Stufe mindestens 28 und maximal 84 tägliche
Dosierungseinheiten umfaßt,
 - die erste Stufe 28 tägliche Dosierungseinheiten umfaßt.
 - die erste Stufe 28 plus 7 oder 28 plus ein Mehrfaches von 7 tägliche
10 Dosierungseinheiten umfaßt,
 - die zweite Stufe 7 tägliche Dosierungseinheiten umfaßt.
 - die erste Stufe 25 oder 26 tägliche Dosierungseinheiten und die zweite
Stufe 5 oder 6 tägliche Dosierungseinheiten umfaßt, so daß das
Kombinationspräparat insgesamt 30 oder 31 tägliche
15 Dosierungseinheiten aufweist.

- Die vorliegende Erfindung betrifft des weiteren ein kontrazeptionelles Kit enthaltend mindestens 30 und maximal 84 tägliche, jeweils mindestens einen hormonellen Wirkstoff enthaltende, Dosierungseinheiten mit einer ersten und einer zweiten Stufe,
- 20 welches in seiner ersten Stufe als hormonellen Wirkstoff in Kombination ein Estrogen- und in mindestens zur Ovulationshemmung ausreichender Dosierung ein Gestagenpräparat in einstufiger Ausbildung und in der zweiten Stufe als hormonellen Wirkstoff lediglich ein Estrogenpräparat enthält, wobei die erste Stufe mindestens 25 und maximal 77 diskrete tägliche oder kontinuierliche Dosierungseinheiten und die
25 zweite Stufe 5, 6 oder 7 tägliche diskrete oder kontinuierliche Dosierungseinheiten umfaßt und die Gesamtzahl der Tageseinheiten gleich der Gesamtzahl der Tage des gewünschten, mindestens 30 und maximal 84 Tage langen, Zyklus ist.

- Bevorzugte kontrazeptionelle Kits gemäß vorliegender Erfindung zeichnen sich
- 30 dadurch aus, daß deren

- erste Stufe 25 oder 26 tägliche Dosierungseinheiten umfaßt,
- erste Stufe mindestens 28 und maximal 84 tägliche Dosierungseinheiten umfaßt,
- erste Stufe 28 tägliche Dosierungseinheiten umfaßt,
35 - erste Stufe 28 plus 7 oder 28 plus ein Mehrfaches von 7 täglichen
Dosierungseinheiten umfaßt,
- zweite Stufe 7 tägliche Dosierungseinheiten umfaßt,

- erste Stufe 25 oder 26 tägliche Dosierungseinheiten und deren zweite Stufe 5 oder 6 tägliche Dosierungseinheiten umfaßt, so daß das Kit insgesamt 30 oder 31 tägliche Dosierungseinheiten aufweist.

- 5 In einer weiteren Ausführungsform des erfindungsgemäßen kontraceptionellen Kits befinden sich die Dosierungseinheiten der ersten Stufe teilweise in sich periodisch wiederholenden Untereinheiten, die räumlich und/oder durch andere Markierungen voneinander getrennt sind.
- 10 Vorzugsweise befinden sich die Dosierungseinheiten frühestens ab der 26. täglichen Dosierungseinheit in Untereinheiten, lassen sich die einzelnen Untereinheiten durch Perforierungen oder andere zum Abtrennen geeignete Vorrichtungen voneinander trennen, sind in den separaten Untereinheiten jeweils 7 Dosierungseinheiten enthalten, umfaßt die erste Stufe 28 plus 7 oder 28 plus ein Mehrfaches von 7
- 15 täglichen Dosierungseinheiten und/oder die zweite Stufe 7 tägliche Dosierungseinheiten.

Bei der erfindungsgemäßen kontraceptiven Methode, die sich des beschriebenen Kombinationspräparates bedient, wird in der ersten Stufe beginnend mit dem ersten

20 Zyklustag eine Dosierungseinheit enthaltend ein Estrogen in Kombination mit einer gestagenen Komponente täglich über mindestens 25 und maximal 77 Tage verabreicht. Daran schließt sich die zweite Stufe an, in der über den verbleibenden Zeitraum zum mindestens 30 und maximal 84 Tage umfassenden Zyklus über 5, 6 oder 7 Tage ein Estrogen verabreicht wird. Es wird also an jedem Tag des Zyklus

25 eine einen hormonellen Wirkstoff enthaltende Dosierungseinheit verabreicht.

Bei Einnahme des erfindungsgemäßen Kombinationspräparates wird die Rekrutierung des dominanten Follikels, die im spontanen Zyklus während der ersten 6 Tage des Menstruationszyklus erfolgt, effizient unterdrückt. Somit lassen sich mit dem

30 Kombinationspräparat der vorliegenden Erfindung die Follikelentwicklung unterdrücken und damit Durchbruchsovulationen vermeiden, wodurch die kontraceptive Sicherheit erhöht wird.

Dies ist vor allem bei Einnahmefehlern von eminenter Wichtigkeit, und zwar insbesondere bei hormonalen Kontraceptiva mit niedriger täglicher Ethinylestradiol-

35 Dosismenge. Da bei 25% der Frauen, die die Pille nehmen, Einnahmefehler (Auslassen von Dosierungseinheiten oder Verlängerung des Intervalls auf über 24 Stunden zwischen der täglichen Einnahme zweier Dosierungseinheiten) bekannt sind (Finlay I.G., Scott M.B.G.: Patterns of contraceptive pill-taking in an inner city practice. Br.Med.J. 1986, 293: 601-602), erhöht das erfindungsgemäße

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Kombinationspräparat, wenn es als ovulationshemmendes Mittel verwendet wird, die kontrazeptive Sicherheit. Dies trifft insbesondere bei niedrigst dosierten Präparaten zu.

- 5 Insbesondere aber führt diese höhere Anzahl sowohl estrogen- als auch gestagenhaltiger täglicher Dosierungseinheiten zu einer Zyklusverlängerung und einer geringeren Häufigkeit von Abbruchblutungen.

Die anschließende Stufe, in der über 5, 6 oder 7 Tage Dosierungseinheiten täglich verabreicht werden, die nur eine estrogene Komponente als hormonalen Wirkstoff
10 enthalten, gewährleistet eine Abbruchsblutung und bewirkt eine Stimulierung von Progesteronrezeptoren im Endometrium, wodurch im folgenden Verabreichungszyklus eine verringerte Zwischenblutungsrate verglichen mit herkömmlichen, niedrig dosierten Präparaten erreicht wird.

- 15 In Verbindung mit der verlängerten Phase der Verabreichung estrogen- und gestagenhaltiger Dosierungseinheiten wird so zum Beispiel eine Verlängerung der Menstruationszyklen auf 30 bzw. 31 Tage möglich (Monatsspackung) möglich.

Gemäß der bevorzugten Varianten ist eine beliebiges Herausschieben der
20 Abbruchblutung bis nach dem Tag 77 möglich, die nach dem Absetzen der estrogen- und gestagenhaltiger Dosierungseinheiten einsetzt.

Eine variable Handhabung des Einleitens der Abbruchblutung ist mit dem kontrazeptionellen Kit gemäß vorliegender Erfindung möglich, bei dem sich die
25 Dosierungseinheiten der ersten Stufe, frühestens ab der 26. täglichen Dosierungseinheit, in Untereinheiten befinden, welche sich aufgrund vorhandener Perforierungen oder anderer zum Abtrennen geeigneter Vorrichtungen voneinander trennen lassen.

- 30 Das erfindungsgemäße kontrazeptionelle Kit ist zum Beispiel in Form eines Blisters ausgebildet, bei welchem sich jeweils einzelne Segmente, die vorzugsweise jeweils 7 Dosierungseinheiten der ersten Stufe enthalten, aufgrund von auf der Basisplatte des Blisters angebrachter Perforierungen bequem und einfach abtrennen lassen.

Es ist aber auch möglich, daß die Untereinheiten jeweils als eigene, separate Blister
35 vorliegen oder die beispielsweise 28 Dosierungseinheiten der ersten Stufe in einem ersten Blister und die folgenden Dosierungseinheiten der ersten Stufe in einem zweiten Blister, bei dem sich in der beschriebenen Weise Untereinheiten durch Perforierungen abtrennen lassen.

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Vorzugsweise wird in allen Ausführungsformen der Erfindung das Estrogen der ersten Hormonkomponente ausgewählt aus der Gruppe der Verbindungen

- 5 17 β -Estradiol,
 Ethinylestradiol und
 17 β -Estradiolvalerat

und das Gestagen ausgewählt aus der Gruppe der Verbindungen

- 10 Dienogest
 Gestoden,
 Levonorgestrel,
 Desogestrel,
 3-Ketodesogestrel,
15 Drospironenon,
 Cyptoeronacetat,
 Norgestimat und
 Norethisteron sowie

- 20 das Estrogen der zweiten Hormonkomponente ausgewählt aus der Gruppe der Verbindungen

- 17 β -Estradiol,
 Ethinylestradiol und
25 17 β -Estradiolvalerat.

Vorzugsweise ist in der vorliegenden Erfindung das Estrogen der ersten Hormonkomponente in jeder täglichen Dosierungseinheit in einer Dosis von

- 30 1.0 bis 6.0 mg 17 β -Estradiol,
 0.015 bis 0.025 mg Ethinylestradiol,
 1.0 bis 4.0 mg 17 β -Estradiolvalerat

und das Gestagen in jeder täglichen Dosierungseinheit in einer Dosis von

- 35 1.0 bis 3.0 mg Dienogest
 0.05 bis 0.075 mg Gestoden,
 0.05 bis 0.125 mg Levonorgestrel,
 0.06 bis 0.15 mg Desogestrel,
 0.06 bis 0.15 mg 3-Ketodesogestrel,

10

1.0 bis 3.0 mg Drospironenon,
1.0 bis 2.0 mg Cyproteronacetat,
0.2 mg bis 0.3 mg Norgestimat,
0.35 bis 0.75 mg Norethisteron

5

enthalten.

Die zweite Hormonkomponente enthält das Estrogen in jeder täglichen Dosierungseinheit vorzugsweise in einer Menge von

10

1.0 bis 6.0 mg 17 β -Estradiol,
0.002 bis 0.04 mg Ethinylestradiol,
1.0 bis 4.0 mg 17 β -Estradiolvalerat.

15 Gemäß einer besonders bevorzugten Ausführungsform enthält die zweite Hormonkomponente als Estrogen Ethinylestradiol in jeder täglichen Dosierungseinheit in einer Menge von 0.01 bis 0.015 mg.

Als Estrogen für die erste sowohl als auch die zweite Hormonkomponente kommt in
20 erster Linie Ethinylestradiol oder das natürliche Estradiol in Betracht.

Von den genannten Gestagenen für die zweite Hormonkomponente ist Gestoden hervorzuheben; auch Levonorgestrel ist bevorzugt.

(25 17 β -Estradiolvalerat, welches als Estrogen sowohl in der ersten als auch in der zweiten Hormonkomponente enthalten sein kann, ist nur als ein möglicher Vertreter dieser 17 β -Estradiolester genannt; auch andere derartige, homologe Ester können als estrogene Komponente im Rahmen der vorliegenden Erfindung verwendet werden.

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Das nachfolgende Beispiel dient der näheren Erläuterung der vorliegenden Erfindung:

Beispiel 1:

	Tag	1	2	3	4	5	6	7
	Zusammensetzung	C	C	C	C	C	C	C
5								
	Tag	8	9	10	11	12	13	14
	Zusammensetzung	C	C	C	C	C	C	C
	Tag	15	16	17	18	19	20	21
10	Zusammensetzung	C	C	C	C	C	C	C
	Tag	22	23	24	25			
	Zusammensetzung	C	C	C	C			
15	Tag	26	27	28	29	30		
	Zusammensetzung	E	E	E	E	E		

Beispiel 2:

20								
	Tag	1	2	3	4	5	6	7
	Zusammensetzung	C	C	C	C	C	C	C
	Tag	8	9	10	11	12	13	14
25	Zusammensetzung	C	C	C	C	C	C	C
	Tag	15	16	17	18	19	20	21
	Zusammensetzung	C	C	C	C	C	C	C
30	Tag	22	23	24	25	26		
	Zusammensetzung	C	C	C	C	C		
	Tag	27	28	29	30	31		
	Zusammensetzung	E	E	E	E	E		

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Beispiel 3:

	Tag	1	2	3	4	5	6	7
	Zusammensetzung	C	C	C	C	C	C	C
5	Tag	8	9	10	11	12	13	14
	Zusammensetzung	C	C	C	C	C	C	C
	Tag	15	16	17	18	19	20	21
10	Zusammensetzung	C	C	C	C	C	C	C
	Tag	22	23	24	25			
	Zusammensetzung	C	C	C	C			
15	Tag	26	27	28	29	30	31	
	Zusammensetzung	E	E	E	E	E	E	

Beispiel 4:

20

	Tag	1	2	3	4	5	6	7
	Zusammensetzung	C	C	C	C	C	C	C
	Tag	8	9	10	11	12	13	14
25	Zusammensetzung	C	C	C	C	C	C	C
	Tag	15	16	17	18	19	20	21
	Zusammensetzung	C	C	C	C	C	C	C
30	Tag	22	23	24	25	26	27	28
	Zusammensetzung	C	C	C	C	C	C	C
	Tag	29	30	31	32	33	34	35
	Zusammensetzung	C	C	C	C	C	C	C
35	Tag	36	37	38	39	40	41	42
	Zusammensetzung	C	C	C	C	C	C	C
	Tag	43	44	45	46	47	48	49

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				13			
	Zusammensetzung	C	C	C	C	C	C
	Tag	50	51	52	53	54	55
	Zusammensetzung	C	C	C	C	C	C
5	Tag	57	58	59	60	61	62
	Zusammensetzung	E	E	E	E	E	E

10 Beispiel 5:

	Tag	1	2	3	4	5	6	7
	Zusammensetzung	C	C	C	C	C	C	C
15	Tag	8	9	10	11	12	13	14
	Zusammensetzung	C	C	C	C	C	C	C
	Tag	15	16	17	18	19	20	21
	Zusammensetzung	C	C	C	C	C	C	C
20	Tag	22	23	24	25	26	27	28
	Zusammensetzung	C	C	C	C	C	C	C
	Tag	29	30	31	32	33	34	35
25	Zusammensetzung	C	C	C	C	C	C	C
	Tag	36	37	38	39	40	41	42
	Zusammensetzung	C	C	C	C	C	C	C
30	Tag	43	44	45	46	47	48	49
	Zusammensetzung	C	C	C	C	C	C	C
	Tag	50	51	52	53	54	55	56
	Zusammensetzung	C	C	C	C	C	C	C
35	Tag	57	58	59	60	61	62	63
	Zusammensetzung	C	C	C	C	C	C	C

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				14				
	Tag	64	65	66	67	68	69	70
	Zusammensetzung	C	C	C	C	C	C	C
	Tag	71	72	73	74	75	76	77
5	Zusammensetzung	C	C	C	C	C	C	C
	Tag	78	79	80	81	82	83	84
	Zusammensetzung	E	E	E	E	E	E	E
10								
	Beispiel 6:							
	Tag	1	2	3	4	5	6	7
	Zusammensetzung	C	C	C	C	C	C	C
15	Tag	8	9	10	11	12	13	14
	Zusammensetzung	C	C	C	C	C	C	C
	Tag	15	16	17	18	19	20	21
20	Zusammensetzung	C	C	C	C	C	C	C
	Tag	22	23	24	25	26	27	28
	Zusammensetzung	C	C	C	C	C	C	C
25	Tag	29	30	31	32	33	34	35
	Zusammensetzung	C	C	C	C	C	C	C
	Tag	36	37	38	39	40	41	42
	Zusammensetzung	C	C	C	C	C	C	C
30	Tag	43	44	45	46	47	48	49
	Zusammensetzung	C	C	C	C	C	C	C
	Tag	50	51	52	53	54	55	56
35	Zusammensetzung	E	E	E	E	E	E	E

Tag = Tag des Menstruationszyklus, Tag 1 ist der erste Blutungstag

C = Kombination von Estrogen und Gestagen (= erste Hormonkomponente)

E = Estrogen (= zweite Hormonkomponente), P = Perforierung

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Die Formulierung der Dosierungseinheiten erfolgt konventionell unter Verwendung von für die Herstellung Estrogen-/Gestagen- sowie ausschließlich Estrogen-haltiger Tabletten, Pillen, Dragees, etc. bekannter Hilfsstoffe.

- 5 Das erfindungsgemäße Kombinationspräparat dient der Empfängnisverhütung für die Frau durch Verabreichung der täglichen Dosierungseinheiten der ersten Hormonkomponente über mindestens 25 und maximal 77 Tage, beginnend am Tag eins des Menstruationszyklus (erster Tag der Menstruationsblutung), gefolgt von 5, 6 oder 7 täglichen Dosierungseinheiten der zweiten Hormonkomponente, die
10 ausschließlich ein Estrogen (E) enthalten, während insgesamt mindestens 30 und maximal 84 Tagen im Verabreichungszyklus. Im zweiten (nächsten) Menstruationszyklus wird an dessen Tag eins ohne Einnahmepause mit der Einnahme der ersten Dosierungseinheit der ersten Hormonkomponente einer neuen Verpackungseinheit (Kit) des erfindungsgemäßen pharmazeutischen
15 Kombinationspräparates weiterverfahren.

- Mit diesem Kombinationspräparat kann eine ausgeprägte ovarielle Suppression ohne häufige Follikelanreifung sowie hervorragender Zykluskontrolle bei niedriger täglicher Estrogendosierung, niedriger Gesamttestrogen- sowie niedriger
20 Gesamthormonmenge pro Verabreichungszyklus erreicht werden.

- Die Vorteile dieses über mindestens 30 und höchstens 84 Tage pro Zyklus verabreichten, erfindungsgemäßen Kombinationspräparates (ovulationshemmendes Mittel) gegenüber den bisher beschriebenen Präparaten, insbesondere denen mit einer
25 täglichen Ethinylestradiol-Dosis von weniger als 30µg und solchen mit pillenfreiem Intervall, lassen sich wie folgt charakterisieren:

1. Eine signifikant geringere Häufigkeit von Follikelentwicklungen bei der
30 Anwenderin. Dies bedeutet eine geringere Gefahr von Durchbruchovulationen und damit eine grössere kontrazeptive Zuverlässigkeit insbesondere bei Einnahmefehlern.
2. Die Rekrutierung des dominanten Follikels wird durch die Verlängerung der
35 Einnahme der Kombination wirksam unterdrückt.
3. Die Einnahme von 5, 6 oder 7 täglichen Estrogen-Dosierungseinheiten im Anschluss an die Verabreichung der Kombinationsdosierung der ersten Stufe führt zu einer deutlich verbesserten Zykluskontrolle und zu einer

geringeren Inzidenz von Nebenwirkungen wie Kopfschmerzen im Rahmen des prämenstruellen Syndroms.

4. Andere klinische Symptome, die auf stark fluktuierende endogene
5 Estrogenspiegel zurückzuführen sind, wie beispielsweise Brustspannen, sind
aufgrund der bedeutend stärkeren ovariellen Supprimierung ebenfalls deutlich
verringert.
5. Durch die Blutungsfreiheit (Amenorrhoe) über einen längeren Zeitraum
10 erhöht sich die Akzeptanz durch die Anwenderin; dies gilt insbesondere mit
steigender Zahl der Dosierungseinheiten in der ersten Stufe.
6. Die mit bzw. durch die Blutungen eintretenden negativen Effekte, wie z.B.
Anämie, Krämpfe, Unwohlsein etc. treten seltener auf.
- 15 7. Konstante niedrige Estrogen- und Gestagenspiegel; dadurch Vermeidung
metabolischer Schwankungen und damit einhergehende Verbesserung der
Verträglichkeit.
- 20 8. Eine eventuelle Schwangerschaft aufgrund von Einnahmefehlern wird durch die
nach dem Absetzen der estrogen- und gestagenhaltigen Dosierungseinheiten
dann ausbleibende Abbruchblutung erkennbar.
- 25 Die Formulierung eines Estrogens und Gestagens für die Herstellung eines
erfindungsgemäßen Kombinationspräparates erfolgt vollkommen analog wie es
bereits für herkömmliche orale Kontrazeptiva mit 21tägiger Einnahmedauer der
Wirkstoffe, wie beispielsweise Femovan® (Ethinylestradiol/Gestoden) oder
Microgynon® (Ethinylestradiol/Levonorgestrel) bekannt ist. Die Formulierung der
30 ausschließlich Estrogen-haltigen Dosierungseinheiten kann ebenso ganz analog wie es
für schon erhältliche, zur oralen Anwendung bestimmten Estrogen-haltige Mittel,
beispielsweise ProgynonC®, bekannt ist, durchgeführt werden.
Die Dosierungseinheiten der ersten Stufe des erfindungsgemäßen Präparates können
auch in Form eines Pflasters (transdermale Applikation), eines Implants oder einer
35 anderen Depotformulierung ausgebildet sein und so kontinuierlich appliziert werden.

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Als Verpackungsform für das erfindungsgemäße Kombinationspräparat dient im allgemeinen eine Blisterpackung, die in der erfindungsgemäßen Art ausgebildet ist; jedoch sind auch andere für diesen Zweck bekannte Verpackungsformen denkbar.

- 5 Zur Bestimmung wirkequivalenter Mengen von Ethinylestradiol und 17 β -Estradiol einerseits und verschiedener Gestagene wie Gestoden, Levonorgestrel, Desogestrel und 3-Ketodesogestrel andererseits wird auf die in der EP-A- 0 253 607 gemachten Angaben verwiesen. Weitere Einzelheiten zur Bestimmung von Dosisäquivalenten verschiedener gestagener Wirkstoffe finden sich beispielsweise in "Probleme der
- 10 Dosisfindung: Sexualhormone"; F. Neumann et al. in "Arzneimittelforschung" (Drug Research) 27, 2a, 296 - 318 (1977) sowie in "Aktuelle Entwicklungen in der hormonalen Kontrazeption"; H. Kuhl in "Gynäkologie" 25: 231 - 240 (1992).

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Patentansprüche

1. ~~Zweistufiges pharmazeutisches Kombinationspräparat zur hormonalen~~
5 ~~Kontrazeption enthaltend mindestens 30 tägliche Dosierungseinheiten, welches in~~
~~seiner ersten Stufe als hormonellen Wirkstoff in Kombination ein Estrogen- und in~~
~~mindestens zur Ovulationshemmung ausreichender Dosierung ein Gestagenpräparat~~
~~in einstufiger Ausbildung und in der zweiten Stufe als hormonellen Wirkstoff~~
~~lediglich ein Estrogenpräparat enthält, wobei die erste Stufe mindestens 25 und~~
10 ~~maximal 77 diskrete tägliche oder kontinuierliche Dosierungseinheiten und die zweite~~
~~Stufe 5, 6 oder 7 tägliche diskrete oder kontinuierliche Dosierungseinheiten umfaßt~~
~~und die Gesamtzahl der Tageseinheiten gleich der Gesamtzahl der Tage des~~
~~gewünschten, mindestens 30 und maximal 84 Tage langen, Zyklus ist,~~
- 15 2. Kombinationspräparat nach Anspruch 1, dadurch gekennzeichnet, daß die erste
Stufe 25 oder 26 tägliche Dosierungseinheiten umfaßt.
3. Kombinationspräparat nach Anspruch 1, dadurch gekennzeichnet, daß die erste
Stufe mindestens 28 und maximal 84 tägliche Dosierungseinheiten umfaßt.
- 20 4. Kombinationspräparat nach Anspruch 3, dadurch gekennzeichnet, daß die erste
Stufe 28 tägliche Dosierungseinheiten umfaßt.
5. Kombinationspräparat nach Anspruch 3, dadurch gekennzeichnet, daß die erste
25 Stufe 28 plus 7 oder 28 plus ein Mehrfaches von 7 tägliche Dosierungseinheiten
umfaßt.
6. Kombinationspräparat nach Anspruch 1, dadurch gekennzeichnet, daß die
zweite Stufe 7 tägliche Dosierungseinheiten umfaßt.
- 30 7. Kombinationspräparat nach Anspruch 2, dadurch gekennzeichnet, daß die
zweite Stufe 5 oder 6 tägliche Dosierungseinheiten umfaßt, so daß das
Kombinationspräparat insgesamt 30 oder 31 tägliche Dosierungseinheiten aufweist.
- 35 8. ~~Kombinationspräparat nach einem der vorstehenden Ansprüche 1 bis 7,~~
~~dadurch gekennzeichnet, daß das Estrogen der ersten Stufe aus der Gruppe der~~
~~Verbindungen~~

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Ethinylestradiol und
17 β -Estradiolvalerat

5 und das Gestagen aus der Gruppe der Verbindungen

Dienogest
Gestoden,
Levonorgestrel,
Desogestrel,
3-Ketodesogestrel,
10 Drospironenon,
Cyptoeronacetat,
Norgestimat und
Norethisteron sowie

15 das Estrogen der zweiten Hormonkomponente aus der Gruppe der Verbindungen.

17 β -Estradiol,
Ethinylestradiol und
17 β -Estradiolvalerat

20

ausgewählt ist.

9. Kombinationspräparat nach einem der vorstehenden Ansprüche 1 bis 8,
dadurch gekennzeichnet, daß das Estrogen der ersten Stufe in jeder täglichen
25 Dosierungseinheit in einer Dosis von

1.0 bis 6.0 mg 17 β -Estradiol,
0.015 bis 0.025 mg Ethinylestradiol,
1.0 bis 4.0 mg 17 β -Estradiolvalerat

30

und das Gestagen in jeder täglichen Dosierungseinheit in einer Dosis von

1.0 bis 3.0 mg Dienogest
0.05 bis 0.075 mg Gestoden
0.05 bis 0.125 mg Levonorgestrel
35 0.06 bis 0.15 mg Desogestrel
0.06 bis 0.15 mg 3-Ketodesogestrel
1.0 bis 3.0 mg Drospironenon
1.0 bis 2.0 mg Cyptoeronacetat
0.2 mg bis 0.3 mg Norgestimat

0.35 bis 0.75 mg Norethisteron

enthalten ist.

- 5 10. Kombinationspräparat nach einem der vorstehenden Ansprüche 1 bis 9, dadurch gekennzeichnet, daß in der zweiten Stufe in jeder täglichen Dosierungseinheit eine Menge von

10 1.0 bis 6.0 mg 17 β -Estradiol,
0.002 bis 0.04 mg Ethinylestradiol,
1.0 bis 4.0 mg 17 β -Estradiolvalerat

enthalten ist.

- 15 11. Kontrazeptionelles Kit enthaltend mindestens 30 tägliche, jeweils mindestens einen hormonellen Wirkstoff enthaltende, Dosierungseinheiten mit einer ersten und einer zweiten Stufe,
welches in seiner ersten Stufe als hormonellen Wirkstoff in Kombination ein Estrogen- und in mindestens zur Ovulationshemmung ausreichender Dosierung ein
20 Gestagenpräparat in einstufiger Ausbildung und in der zweiten Stufe als hormonellen Wirkstoff lediglich ein Estrogenpräparat enthält, wobei die erste Stufe mindestens 25 und maximal 77 diskrete tägliche oder kontinuierliche Dosierungseinheiten und die zweite Stufe 5, 6 oder 7 tägliche diskrete oder kontinuierliche Dosierungseinheiten umfaßt und die Gesamtzahl der Tageseinheiten gleich der Gesamtzahl der Tage des
25 gewünschten, mindestens 30 und maximal 84 Tage langen, Zyklus ist.

12. Kontrazeptionelles Kit nach Anspruch 11, dadurch gekennzeichnet, daß dessen erste Stufe 25 oder 26 tägliche Dosierungseinheiten umfaßt.

- 30 13. Kontrazeptionelles Kit nach Anspruch 11, dadurch gekennzeichnet, daß die erste Stufe mindestens 28 und maximal 84 tägliche Dosierungseinheiten umfaßt.

14. Kontrazeptionelles Kit nach Anspruch 13, dadurch gekennzeichnet, daß die erste Stufe 28 tägliche Dosierungseinheiten umfaßt.

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15. Kontrazeptionelles Kit nach Anspruch 13, dadurch gekennzeichnet, daß die erste Stufe 28 plus 7 oder 28 plus ein Mehrfaches von 7 tägliche Dosierungseinheiten umfaßt.

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16. Kontrazeptionelles Kit nach Anspruch 11, dadurch gekennzeichnet, daß die zweite Stufe 7 tägliche Dosierungseinheiten umfaßt.
17. Kontrazeptionelles Kit nach Anspruch 12, dadurch gekennzeichnet, daß die
5 zweite Stufe 5 oder 6 tägliche Dosierungseinheiten umfaßt, so daß das Kit insgesamt 30 oder 31 tägliche Dosierungseinheiten aufweist.
18. Kontrazeptionelles Kit nach einem der vorstehenden Ansprüche 11 bis 17,
dadurch gekennzeichnet, daß das Estrogen der ersten Stufe aus der Gruppe der
10 Verbindungen

17 β -Estradiol,
Ethinylestradiol und
17 β -Estradiolvalerat

15

und das Gestagen aus der Gruppe der Verbindungen

Dienogest
Gestoden,
Levonorgestrel,
20 Desogestrel,
3-Ketodesogestrel,
Drospironenon,
Cyptoeronacetat,
Norgestimat und
25 Norethisteron sowie

20

25

das Estrogen der zweiten Hormonkomponente aus der Gruppe der Verbindungen.

17 β -Estradiol,
30 Ethinylestradiol und
17 β -Estradiolvalerat

30

ausgewählt ist.

- 35 19. Kontrazeptionelles Kit nach einem der vorstehenden Ansprüche 11 bis 18,
dadurch gekennzeichnet, daß das Estrogen der ersten Stufe in jeder täglichen
Dosierungseinheit in einer Dosis von

1.0 bis 6.0 mg 17 β -Estradiol,

0.015 bis 0.025 mg Ethinylestradiol,
1.0 bis 4.0 mg 17 β -Estradiolvalerat

und das Gestagen in jeder täglichen Dosierungseinheit in einer Dosis von

- 5 1.0 bis 3.0 mg Dienogest
 0.05 bis 0.075 mg Gestoden
 0.05 bis 0.125 mg Levonorgestrel
 0.06 bis 0.15 mg Desogestrel
 0.06 bis 0.15 mg 3-Ketodesogestrel
10 1.0 bis 3.0 mg Drospironenon
 1.0 bis 2.0 mg Cyptoeronacetat
 0.2 mg bis 0.3 mg Norgestimat
 0.35 bis 0.75 mg Norethisteron

15 enthalten ist.

20. Kontrazeptionelles Kit nach einem der vorstehenden Ansprüche 11 bis 19, dadurch gekennzeichnet, daß in der zweiten Stufe in jeder täglichen Dosierungseinheit eine Menge von

- 20 1.0 bis 6.0 mg 17 β -Estradiol,
 0.002 bis 0.04 mg Ethinylestradiol,
 1.0 bis 4.0 mg 17 β -Estradiolvalerat

25 enthalten ist.

21. Kontrazeptionelles Kit enthaltend mindestens 30 tägliche, jeweils mindestens einen hormonellen Wirkstoff enthaltende, Dosierungseinheiten mit einer ersten und einer zweiten Stufe,

- 30 welches in seiner ersten Stufe als hormonellen Wirkstoff in Kombination ein Estrogen- und in mindestens zur Ovulationshemmung ausreichender Dosierung ein Gestagenpräparat in einstufiger Ausbildung und in seiner zweiten Stufe als hormonellen Wirkstoff lediglich ein Estrogenpräparat enthält, wobei die erste Stufe mindestens 25 und maximal 77 diskrete tägliche oder kontinuierliche
35 Dosierungseinheiten und die zweite Stufe 5, 6 oder 7 tägliche diskrete oder kontinuierliche Dosierungseinheiten umfaßt und die Gesamtzahl der Tageseinheiten gleich der Gesamtzahl der Tage des gewünschten, mindestens 30 und maximal 84 Tage langen, Zyklus ist,

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23

wobei sich die Dosierungseinheiten der ersten Stufe teilweise in sich periodisch wiederholenden Untereinheiten befinden, die räumlich und/oder durch andere Markierungen voneinander getrennt sind.

- 5 22. Kontrazeptionelles Kit nach Anspruch 21, dadurch gekennzeichnet, daß sich die Dosierungseinheiten frühestens ab der 26. täglichen Dosierungseinheit in Untereinheiten befinden.
- 10 23. Kontrazeptionelles Kit nach Anspruch 21 oder 22, dadurch gekennzeichnet, daß sich die einzelnen Untereinheiten durch Perforierungen oder andere zum Abtrennen geeignete Vorrichtungen voneinander trennen lassen.
- 15 24. Kontrazeptionelles Kit nach einem der Ansprüche 21, 22 oder 23, dadurch gekennzeichnet, daß die separaten Untereinheiten jeweils 7 Dosierungseinheiten enthalten.
- 20 25. Kontrazeptionelles Kit nach einem der vorstehenden Ansprüche 21 bis 24, dadurch gekennzeichnet, daß die erste Stufe 28 plus 7 oder 28 plus ein Mehrfaches von 7 tägliche Dosierungseinheiten umfaßt.
26. Kontrazeptionelles Kit nach einem der vorstehenden Ansprüche 21 bis 25, dadurch gekennzeichnet, daß die zweite Stufe 7 tägliche Dosierungseinheiten umfaßt.
- 25 27. Kontrazeptionelles Kit nach einem der vorstehenden Ansprüche 21 bis 26, dadurch gekennzeichnet, daß das Estrogen der ersten Stufe aus der Gruppe der Verbindungen

30 17 β -Estradiol,
Ethinylestradiol und
17 β -Estradiolvalerat

und das Gestagen aus der Gruppe der Verbindungen

35 Dienogest
Gestoden,
Levonorgestrel,
Desogestrel,
3-Ketodesogestrel,
Drospironenon,
Cytoeronacetat,

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Norgestimat und
Norethisteron sowie

das Estrogen der zweiten Hormonkomponente aus der Gruppe der Verbindungen.

5

17 β -Estradiol,
Ethinylestradiol und
17 β -Estradiolvalerat

10 ausgewählt ist.

28. Kontrazeptionelles Kit nach einem der vorstehenden Ansprüche 21 bis 27, dadurch gekennzeichnet, daß das Estrogen der ersten Stufe in jeder täglichen Dosierungseinheit in einer Dosis von

15

1.0 bis 6.0 mg 17 β -Estradiol,
0.015 bis 0.025 mg Ethinylestradiol,
1.0 bis 4.0 mg 17 β -Estradiolvalerat

20 und das Gestagen in jeder täglichen Dosierungseinheit in einer Dosis von

1.0 bis 3.0 mg Dienogest
0.05 bis 0.075 mg Gestoden
0.05 bis 0.125 mg Levonorgestrel
0.06 bis 0.15 mg Desogestrel
0.06 bis 0.15 mg 3-Ketodesogestrel
1.0 bis 3.0 mg Drospironenon
1.0 bis 2.0 mg Cyptoeronacetat
0.2 mg bis 0.3 mg Norgestimat
0.35 bis 0.75 mg Norethisteron

25

30

enthalten ist.

29. Kontrazeptionelles Kit nach einem der vorstehenden Ansprüche 21 bis 28, dadurch gekennzeichnet, daß in der zweiten Stufe in jeder täglichen
35 Dosierungseinheit eine Menge von

1.0 bis 6.0 mg 17 β -Estradiol,
0.002 bis 0.04 mg Ethinylestradiol,
1.0 bis 4.0 mg 17 β -Estradiolvalerat

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enthalten ist.

30. Methode zur Kontrazeption bei weiblichen Säugetieren umfassend eine
5 mindestens 30 und maximal 84tägige sequentielle Gabe täglicher Dosierungseinheiten
von mindestens 25 und maximal 77 diskreter täglicher oder kontinuierlicher
Dosierungseinheiten während einer ersten Stufe und 5, 6 oder 7 täglicher diskreter
oder kontinuierlicher Dosierungseinheiten während einer zweiten Stufe enthaltend in
der ersten Stufe als hormonellen Wirkstoff in Kombination ein Estrogen- und in
10 mindestens zur Ovulationshemmung ausreichender Dosierung ein Gestagenpräparat
in einstufiger Ausbildung und in der zweiten Stufe als hormonellen Wirkstoff
lediglich ein Estrogenpräparat.
31. Methode nach Anspruch 30, dadurch gekennzeichnet, daß in der ersten Stufe
15 25 oder 26 tägliche Dosierungseinheiten gegeben werden.
32. Methode nach Anspruch 30, dadurch gekennzeichnet, daß in der ersten Stufe
mindestens 28 und maximal 77 tägliche Dosierungseinheiten gegeben werden.
- 20 33. Methode nach Anspruch 32, dadurch gekennzeichnet, daß in der ersten Stufe
28 tägliche Dosierungseinheiten gegeben werden.
34. Methode nach Anspruch 32, dadurch gekennzeichnet, daß in der ersten Stufe
28 plus 7 oder 28 plus ein Mehrfaches von 7 tägliche Dosierungseinheiten gegeben
25 werden.
35. Methode nach einem der vorstehenden Ansprüche 30 bis 34, dadurch
gekennzeichnet, daß in der zweiten Stufe 7 tägliche Dosierungseinheiten gegeben
werden.
30
36. Methode nach Anspruch 31, dadurch gekennzeichnet, daß in der zweiten Stufe
5 oder 6 tägliche Dosierungseinheiten gegeben werden.
37. Methode nach einem der vorstehenden Ansprüche 30 bis 36, dadurch
35 gekennzeichnet, daß das Estrogen in den Dosierungseinheiten der ersten Stufe aus der
Gruppe der Verbindungen

17 β -Estradiol,
Ethinylestradiol und

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17 β -Estradiolvalerat

und das Gestagen aus der Gruppe der Verbindungen

5 Dienogest
 Gestoden,
 Levonorgestrel,
 Desogestrel,
 3-Ketodesogestrel,
10 Drospironenon,
 Cyptoeronacetat,
 Norgestimat und
 Norethisteron sowie

das Estrogen in den Dosierungseinheiten der zweiten Hormonkomponente aus der
15 Gruppe der Verbindungen.

 17 β -Estradiol,
 Ethinylestradiol und
 17 β -Estradiolvalerat

20 ausgewählt ist.

38. Methode nach einem der vorstehenden Ansprüche 30 bis 37, dadurch
gekennzeichnet, daß das Estrogen der ersten Stufe in jeder täglichen
25 Dosierungseinheit in einer Dosis von

 1.0 bis 6.0 mg 17 β -Estradiol,
 0.015 bis 0.025 mg Ethinylestradiol,
 1.0 bis 4.0 mg 17 β -Estradiolvalerat

30 und das Gestagen in jeder täglichen Dosierungseinheit in einer Dosis von

 1.0 bis 3.0 mg Dienogest
 0.05 bis 0.075 mg Gestoden
 0.05 bis 0.125 mg Levonorgestrel
35 0.06 bis 0.15 mg Desogestrel
 0.06 bis 0.15 mg 3-Ketodesogestrel
 1.0 bis 3.0 mg Drospironenon
 1.0 bis 2.0 mg Cyptoeronacetat
 0.2 mg bis 0.3 mg Norgestimat

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27

0.35 bis 0.75 mg Norethisteron

gegeben wird.

- 5 39. Methode nach einem der vorstehenden Ansprüche 30 bis 38, dadurch gekennzeichnet, daß in der zweiten Stufe in jeder täglichen Dosierungseinheit eine Menge von

10 1.0 bis 6.0 mg 17 β -Estradiol,
0.002 bis 0.04 mg Ethinylestradiol,
1.0 bis 4.0 mg 17 β -Estradiolvalerat

gegeben wird.

- 15 40. Methode nach einem der Ansprüche 30 bis 39 worin das weibliche Säugetier ein homo sapiens sapiens ist.