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FORMULARIO UNICO DE OPOSICION
2000-12

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OPOSICION A:

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

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**SOLICITUD
PUBLICADA**

Número del expediente: 05 130.115

Solicitante: GADOR S.A.

Apoderado: JORGE E. VERA VARGAS

Título de la nueva creación o denominación del signo:

"COMPOSICIONES FARMACÉUTICAS SÓLIDAS QUE COMPRENDEN UNA COMBINACIÓN DE DROSPIRENONA, ETINILESTRADIOL Y UN AGENTE SURFACTANTE ADECUADO QUE PRESENTA UNA HOMOGENEIDAD DE CONTENIDO Y VELOCIDAD DE DISOLUCIÓN ASEGURADA PARA LA DROGA NO MICRONIZADA, PROCEDIMIENTO PARA PREPARAR DICHA COMPOSICIÓN Y USO DE ESTA COMPOSICIÓN PARA PREPARAR UN MEDICAMENTO."

Gaceta: 577 de 29 de junio de 2007, Número de Publicación 93.

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OPOSICION PRESENTADA POR:

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FUNDAMENTOS DE LA OPOSICION:

Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000). Se violan los artículos 14, 16 (las patentes de invención deben ser nuevas, tener nivel inventivo y ser susceptibles de aplicación industrial) 18 (una invención tiene nivel inventivo si no es obvia para una persona versada en la materia).

Justificación: VER ANEXO

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Comprobante de pago No. 07-78.570 (Oposición) Fecha Septiembre 22 de 2003
07-78.582 (Prórroga) Fecha Septiembre 22 de 2003

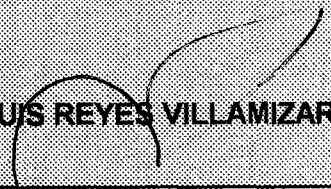
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Anexos:

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

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NOMBRE: JOSÉ LUIS REYES VILLAMIZAR

FIRMA: 

C.C.No. 79.152.473 T.P. No. 44655

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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF:

EXPEDIENTE 05-130-115

TÍTULO SOLICITADO:

"COMPOSICIONES FARMACÉUTICAS SÓLIDAS QUE COMPRENDEN UNA COMBINACIÓN DE DROSPIRENONA, ETINILESTRADIOL Y UN AGENTE SURFACTANTE ADECUADO QUE PRESENTA UNA HOMOGENEIDAD DE CONTENIDO Y VELOCIDAD DE DISOLUCIÓN ASEGURADA PARA LA DROGA NO MICRONIZADA, PROCEDIMIENTO PARA PREPARAR DICHA COMPOSICIÓN Y USO DE ESTA COMPOSICIÓN PARA PREPARAR UN MEDICAMENTO."

PUBLICACIÓN:

Gaceta 577 de 29 de Junio de 2007, número de publicación 93

SOLICITANTE:

GADOR S.A.

PRIORIDAD:

AR P04 01 04928 del 28/12/2004.

APODERADO:

JORGE E. VERA VARGAS

TRÁMITE:

PRESENTACIÓN DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LAFRANCOL S.A.**, en desarrollo de lo dispuesto por los artículos 42 y siguientes de la Decisión 486 de 2000 de la Comunidad Andina de Naciones, me permito solicitarle, muy respetuosamente, dar curso a la siguiente

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I. PETICIÓN

Negar el beneficio patentario a la solicitud contenida en el expediente **05-130-115**, por no cumplir con los requisitos de patentabilidad a que se refieren los artículos 14, 16 y 18 de la Decisión 486 de la Comunidad Andina de Naciones, con base en los fundamentos de hecho y de derecho que me permito exponer a continuación.

II. LEGÍTIMO INTERÉS

Asiste a **LAFRANCOL S.A.** legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias y composiciones farmacéuticas carentes de nivel inventivo, en detrimento de sus legítimos intereses comerciales y de la libre competencia.

III. FUNDAMENTOS DE LA OPOSICIÓN

La solicitud colombiana de la referencia que se encuentra actualmente en trámite, y que revela una composición farmacéutica contraceptiva para administración oral (tipo cápsula dura o comprimido) conteniendo una combinación terapéuticamente efectiva de los principios activos Etinil Estradiol y Drospirenona junto a agentes surfactantes no iónicos, carece de novedad y de nivel inventivo si se tienen en cuenta los siguientes argumentos:

3.1. La combinación farmacológica de la reivindicación 1 y subsiguientes entre drospirenona y etinil estradiol, sus rangos de dosificación y su uso como alternativa anticonceptiva es reconocida y ampliamente estudiada dentro del estado de la técnica, tal y como lo demuestran las siguientes publicaciones de carácter científico:

3.1.1. An open-label, multicenter study to evaluate Yasmin, a low-dose combination oral contraceptive containing drospirenone, a new progestogen¹.

Resumen: This open-label, multicenter study evaluated the efficacy, safety, and cycle control of Yasmin, a new low-dose, monophasic oral contraceptive

¹ An open-label, multicenter study to evaluate Yasmin, a low-dose combination oral contraceptive containing drospirenone, a new progestogen. (eng; includes abstract) By Parsey KS, Contraception [Contraception], 2000 Feb; Vol. 61 (2), pp. 105-11; PMID: 10802275

containing the unique progestogen drospirenone (DRSP) 3 mg and ethinyl estradiol (EE) 30 microg. DRSP is a synthetic progestogen that has antiandrogenic and antimineralocorticoid effects. In this study, 326 women were evaluated and 220 (67%) completed all 13 treatment cycles. The corrected Pearl Index was 0.407. Of the 151 subjects who experienced intermenstrual bleeding at any time during the study, the majority (64%) had bleeding during only one or two pill cycles. Breakthrough bleeding without spotting occurred in 1% of all cycles, spotting without breakthrough bleeding in 9.3% of all cycles, and breakthrough bleeding with spotting in 3% of all cycles. Amenorrhea was observed in 3% of all cycles. In all, 20 subjects (6%) discontinued participation in the study because of adverse events. No serious adverse events related to the study drug were reported. No clinically significant changes in weight, blood pressure, or lipids were reported. The impact of the new progestogen DRSP on the women's self-perception of menstrual health was also evaluated. Subjects reported that symptoms of water retention, negative affect, and increased appetite significantly improved at cycle 6 from baseline. This study demonstrates that Yasmin is an effective oral contraceptive that is safe and well tolerated.

3.1.2. Drospirenone: pharmacology and pharmacokinetics of a unique progestogen².

Resumen: The pharmacology and pharmacokinetics of drospirenone, a unique progestogen, are reviewed in this paper. Unlike other progestogens, drospirenone, an analogue of spironolactone, has biochemical and pharmacologic profiles similar to endogenous progesterone, especially regarding antimineralocorticoid and antiandrogenic activities. Drospirenone counteracts the estrogen-induced stimulation of the renin-angiotensin-aldosterone system and blocks testosterone from binding to androgen receptors. Because of these characteristics, it has the potential to reduce body weight, blood pressure, and low-density lipoprotein levels and to enhance high-density lipoprotein levels. As a combination oral contraceptive, drospirenone with ethinyl estradiol is effective and has positive effects on weight and lipid levels. Additionally, it relieves menstrually related symptoms (e.g., negative affect and water retention) that are commonly observed with other combination oral contraceptives. Based on the biochemical and pharmacodynamic data, drospirenone appears to be a viable alternative to the currently available progestogens.

3.1.3. Effect of a combined oral contraceptive containing 3 mg of drospirenone and 30 microg of ethinyl estradiol on the human endometrium³.

Resumen: OBJECTIVE: To provide an in-depth assessment of the effects of the combined oral contraceptive containing 30 microg of ethinyl estradiol and 3 mg of drospirenone (Yasmin, Schering AG, Berlin) on the endometrium by

² Drospirenone: pharmacology and pharmacokinetics of a unique progestogen. (eng; includes abstract) By Krattenmacher R, Contraception [Contraception], 2000 Jul; Vol. 62 (1), pp. 29-38; PMID: 11024226

³ Effect of a combined oral contraceptive containing 3 mg of drospirenone and 30 microg of ethinyl estradiol on the human endometrium. (eng; includes abstract) By Lüdike F, Fertility And Sterility [Fertil Steril], 2001 Jul; Vol. 76 (1), pp. 102-7; PMID: 11438327

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means of endometrial morphometry in comparison to an untreated cycle.

DESIGN: The open, multicenter study consisted of one untreated precycle and 13 treatment cycles. **SETTING:** Four gynecologic clinics in Belgium, The Netherlands, and Switzerland were involved. **PATIENT(S):** Forty women with a history of regular menstrual cycles. **INTERVENTION(S):** Before the commencement of the trial, 3 months without any hormonal intake was obligatory. The first endometrial sample was done in the untreated precycle, adjusted to the day of LH peak plus 5 to 6 days. During the medication phase, endometrial samples were taken at cycle 3, 6 and 13. **MAIN OUTCOME MEASURE(S):** Primary outcome measure of the study was the morphologic assessment of the endometrium with measures such as glandular diameter, glandular epithelial height, and number of vacuolated cells per 1,000 glandular cells. Furthermore, the endometrial thickness was measured by ultrasound. **RESULT(S):** After 13 cycles of medication use the endometrium had an atrophic appearance in 63% of the subjects. The size of the glands, the glandular epithelial height, and the number of glands per square millimeter were already significantly reduced after 3 months' use. Histological and ultrasonographical evaluation of the endometrium indicated a suppression of the proliferative activity of the endometrium. **CONCLUSION(S):** The combination of 30 microg of ethinyl estradiol with 3 mg of drospirenone induces changes of the endometrium that are comparable with other combined oral contraceptives and exhibits a marked antiproliferative effect on the endometrium. The medication was proven to be an effective oral contraceptive and revealed good cycle control characteristics.

3.1.4. New Monophasic Oral Contraceptive Containing Drospirenone Decreases Premenstrual Symptoms⁴.

Resumen: According to researchers, an oral contraceptive containing drospirenone (DRSP) in combination with ethinyl estradiol (EE) may be more effective in reducing premenstrual symptoms than other combined oral contraceptives. The present study demonstrated that DRSP/EE consistently improved mood symptoms in a mildly symptomatic population. The most striking reductions in symptoms among all subjects, new users and switchers, occurred in irritability and mood swings during the premenstrual and menstrual phases.

3.1.5. A comparative study of monophasic oral contraceptives containing either drospirenone 3 mg or levonorgestrel 150 µg on premenstrual symptoms⁵.

Resumen: This open-label randomized study compared the effects of two combined oral contraceptives (OCs) containing 3 mg drospirenone (DRSP)/30 µg ethinyl estradiol (EE) with 150 µg levonorgestrel (LNG)/30 µg EE on the prevalence and changes from baseline of premenstrual symptoms after six cycles. The symptoms were measured using the Women's Health Assessment Questionnaire. Subjects receiving DRSP/EE had fewer prevalence of

⁴ New Monophasic Oral Contraceptive Containing Drospirenone Decreases Premenstrual Symptoms. Fertility Weekly, 3/18/2002, p18-19, 2p; (AN 11917026)

⁵ A comparative study of monophasic oral contraceptives containing either drospirenone 3 mg or levonorgestrel 150 µg on premenstrual symptoms. By: Sangthawan, Malinee; Taneepanichkul, Surasak. Contraception, Jan2005, Vol. 71 Issue 1, p1-7, 7p; DOI: 10.1016/j.contraception.2004.07.010; (AN 17245955)

premenstrual symptoms than those receiving LNG/EE after six cycles. A significantly lower score of negative affect category in the premenstrual phase was demonstrated in those receiving DRSP/EE more than LNG/EE. The DRSP/EE group showed a greater improvement of mean scores from baseline in the premenstrual phase compared with those who received LNG/EE on negative affect as seen in the items on anxiety, irritability, feeling sad or blue and weight gain in the category of water retention. In conclusion, OCs containing DRSP have beneficial effects in reducing the prevalence of premenstrual symptoms especially the symptoms of negative affect and weight gain, particularly when compared to LNG/EE. Hence, it should be recommended for women who are susceptible to these adverse symptoms.

3.1.6. Evaluation of a Unique Oral Contraceptive in the Treatment of Premenstrual Dysphoric Disorder⁶.

Resumen: Premenstrual dysphoric disorder (PMDD) is a severe form of premenstrual syndrome (PMS). This is the first trial of a unique oral contraceptive containing a combination of drospirenone (DRSP, 3 mg) and ethinyl estradiol (EE, 30 µg) for the treatment of PMDD. DRSP is a spironolactone-like progestin with antiandrogenic and antimineralocorticoid activity. Spironolactone has been shown to be beneficial in PMS, whereas oral contraceptives have shown conflicting results. In this double-blind, placebo-controlled trial, 82 women with PMDD (Diagnostic and Statistical Manual of Mental Disorders, 4th ed. [DSM IV]) were randomized to receive DRSP/EE or placebo for three treatment cycles. The primary end point was change from baseline in luteal phase symptom scores as assessed on the Calendar of Premenstrual Experiences (COPE) scale. Patients treated with DRSP/EE showed a numerically greater change from baseline compared with those treated with placebo on each of the 22 COPE items and each of the 4 symptom factors. Between-group differences in symptom improvement reached statistical significance in factor 3 only (appetite, acne, and food cravings, $p = 0.027$). The secondary end points, Beck Depression Inventory (BDI) and Profile of Mood States (PMS), were consistent with the primary end point in that patients treated with the oral contraceptive showed a numerically greater improvement from baseline compared with those treated with placebo. The results of this study show a consistent trend in the reduction of symptoms that suggested a beneficial effect of DRSP/EE for the treatment of PMDD, despite limitations of the study design.

3.1.7. Eficacia y Tolerancia de un Anticonceptivo Monofásico Oral con Estradiol y Drospirenona⁷.

Resumen: La combinación de 30 g de etinilestradiol y 3 mg de drospirenona provee una efectiva anticoncepción oral, excelente control del ciclo, buena tolerancia y disminución de peso corporal que mejora el cumplimiento del tratamiento.

⁶ Evaluation of a Unique Oral Contraceptive in the Treatment of Premenstrual Dysphoric Disorder. By: Freeman, Ellen W.; Kroik, Robin; Rapkin, Andrea; Pearlstein, Teri; Brown, Candace; Parsey, Kelly; Zhang, Paul; Patel, Harji; Foegh, Marie. Journal of Women's Health & Gender-Based Medicine, Jul2001, Vol. 10 Issue 6, p561-569, 9p, 3 graphs, 2bw; DOI: 10.1089/15246090152543148; (AN 5323805)

⁷ Huber J, Foidart J, Wuttke W y colaboradores. 7. Eficacia y Tolerancia de un Anticonceptivo Monofásico Oral con Estradiol y Drospirenona. The European Journal of Contraception and Reproductive Health Care 5(1):25-34, Mar 2000.

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Luego de lo consignado hasta el momento y si nos referimos específicamente a la combinación de estos dos principios activos (Drospirenona y Etinil estradiol), a su forma de administración (tabletas y cápsulas duras) y las cantidades o rangos dentro de la formulación es evidente la falta de novedad de la solicitud colombiana en trámite.

De la misma forma, existen documentos que evidencian la anterioridad en la formulación y forma de dosificación de esta combinación farmacológica, tal y como se muestra a continuación:

3.1.8. La publicación internacional WO 98/04268 publicada el 05 de Febrero de 1998 y titulada "ORAL CONTRACEPTIVE" revela:

This invention provides a triphasic 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

(...)

comprises administering to a female of child bearing age a first phase of a combination of a progestin at a daily dosage of 40-500 µg trimegestone, 250 µg - 4 mg dienogest, or 250 µg - 4 mg drospirenone, and an estrogen at a daily dosage equivalent in estrogenic activity to 10-20 µg ethinyl estradiol for 3-8 days beginning on day 1 of the menstrual cycle. The same daily dosage of the progestin and estrogen is administered for each of the 3-8 days. A second phase of a combination of a progestin at a daily dosage of 40-500 µg trimegestone, 250 µg - 4 mg dienogest, or 250 µg - 4 mg drospirenone, and an estrogen at a daily dosage equivalent in estrogenic activity to 10-20 µg ethinyl estradiol

(...)

Preferred estrogens include, but are not limited to ethinyl estradiol; 17β-estradiol; conjugated estrogens, USP; estrone or a salt thereof; and mestranol; with ethinyl estradiol being more preferred. Preferred salts of estrone include, but are not

(...)

The following daily dosages of a combination of drospirenone and ethinyl estradiol are preferred for contraception when administered according to a triphasic mid-peak regimen for 23-25 consecutive days beginning on the first day of menses, with 24 days being preferred. The preferred phase lengths are provided above. Of the

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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

(...)

3.1.9. La publicación internacional WO 99/13882 publicada el 25 de Marzo de 1999 y titulada "ORAL CONTRACEPTIVE PREPARATION HAVING A FIRST PHASE PROGESTIN/ESTROGEN AND A SECOND PHASE COMPRISING PROGESTIN" Revela:

This invention provides a progestin bridged 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 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 a progestin 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.

(...)

Preferred progestins include, but are not limited to levonorgestrel, norgestrel, desogestrel, 3-ketodesogestrel, norethindrone, gestodene, norethisterone acetate, norgestimate, osaterone, cyproterone acetate, trimegestone, dienogest, and drospirenone. It is more preferred that the progestin is levonorgestrel. When

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Drospirenone	500 µg - 3.75 mg	100 µg - 2.5 mg
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Preferred estrogens include, but are not limited to ethinyl estradiol; 17β-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 the preferred daily dosage is 10-20 µg, with 15 µg being more preferred. When 17β-

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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

3.1.10. La patente americana US 6,451,778 publicada el 17 de Septiembre de 2002 y titulada "ORAL CONTRACEPTIVE" Revela:

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

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More particularly, this invention provides a method of contraception which comprises administering to a female of child bearing age 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 equivalent in estrogenic activity to 10–20 μg ethinyl estradiol for 23–25 days beginning on day 1 of the menstrual cycle. Following the 23–25-

(...)

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 μg , with 15 μg being more preferred.

(...)

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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3.1.11. La publicación internacional WO 02/094281 publicada el 28 de Noviembre de 2002 y titulada "MEANS AND METHOD FOR HORMONAL CONTRACEPTION" Revela:

One embodiment of the present invention is concerned with a kit containing a plurality of daily hormone units for use in a contraceptive method, the plurality of daily hormone units consisting of:

- a) one or more daily hormone units containing synthetic estrogen or a combination of synthetic estrogen and biogenic estrogen in an amount equivalent to 3-40 µg ethinyl estradiol and

(...)

The synthetic estrogen present in the kit according to the invention is preferably selected from the group consisting of: ethinyl estradiol, mestranol, quinestranol, precursors capable of liberating such an estrogen when used in the present contraceptive method and mixtures thereof. Most preferably the synthetic estrogen is ethinyl estradiol or a precursor

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The progestogen contained in the kit of the invention is preferably selected from the group consisting of levonorgestrel, norgestimate, norethisterone, dydrogesterone, drospirenone, 3-beta-hydroxydesogestrel, 3-keto desogestrel (=etonogestrel), 17-deacetyl

(...)

ethyl-17alpha-ethinyl-gon-4-en-3-one oxime and precursors of these compounds. Preferably the progestogen used in the progestogenic phase is selected from the group consisting of levonorgestrel, norgestimate, norethisterone, drospirenone, dydrogesterone and their precursors

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Generally speaking, the hormone units in the present kit are prepared according to conventionally known procedures in accordance with the method of administration. Thus, the active ingredients are prepared according to known methods in a pharmaceutically acceptable form for administration. These ingredients, in their required quantities are combined with the appropriate pharmaceutical carriers such as additives, vehicles and/or flavour ameliorating substances. These substances may be referred to as diluents, binders and lubricants. Gums, starches and sugars are also common terms. Typical of these types of substances or excipients are pharmaceutical grades of mannitol, lactose starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate and the like. The active ingredient(s) may comprise from about 0.01% by weight to about 99.99% by weight of the total formulation and the remainder comprises the pharmaceutically acceptable carrier. The

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Thus, the active ingredients are compounded with the chosen carrier and in for example the case of a tablet form, placed in a tablet moulding apparatus to form the tablets which are subsequently packaged in accordance with the chosen regimen.

Además reivindica:

6. A kit according to any one of claims 2-5, wherein the daily hormone units for use during the estrogenic phase contain the synthetic estrogen in an amount equivalent to 3-40 µg, preferably 15-40 µg ethinyl estradiol.

11. A kit according to any one of claims 1-10, wherein the progestogen is selected from the group consisting of levonorgestrel, norgestimate, norethisterone, dydrogesterone, drospirenone, 3-beta-hydroxydesogestrel, etonogestrel, 17-deacetyl norgestimate, 19-norprogesterone, acetoxypregnenolone, allylestrenol, anagestone, chlormadinone,

12. A kit according to any one of claims 1-11, wherein the hormone units for use during the estrogenic phase contain ethinyl estradiol or a combination of ethinyl estradiol and estradiol and/or precursors thereof in a therapeutically effective amount to inhibit ovulation and the hormone units for use during the progestogenic phase contain a combination of estradiol and/or a precursor thereof and a progestogen selected from the group consisting of levonorgestrel, norgestimate, norethisterone, drospirenone, dydrogesterone and their precursors, in a therapeutically effective amount to inhibit ovulation and to transform the endometrium from a proliferative into a secretory state.

3.1.12. La patente americana US 6,667,050 publicada el 23 de Diciembre de 2003 y titulada "CHEWABLE ORAL CONTRACEPTIVE" Revela:

The present invention relates to chewable, palatable oral contraceptive tablets for administering an oral contraceptive agent to human females. The tablets of this invention may simply be chewed, and therefore are easy for a patient to ingest, even in the absence of a liquid. The oral contraceptive agent formulation of this invention improves dosage regimen compliance, and thereby enhances the desired contraceptive effect of the oral contraceptive. This invention also includes methods for administering the oral contraceptive formulations to a woman.

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The term "estrogen," as used herein, refers to any natural or synthetic compound which exhibits an effect on the female reproductive organs in a manner similar to the natural female hormone estrogen. Examples of an estrogen include, but are not limited to, ethinyl estradiol, estradiol, estradiol valerate, and estradiol acetate.

(...)

The term "progestin," as used herein, refers any natural or synthetic compound which exhibits a progestational effect on the female reproductive organs. Examples of a progestin include, but are not limited to, norethindrone, norethindrone acetate, desogestrel, levonorgestrel, ethynodiol diacetate, norgestrel, norgestimate, gestodene, drospirenone, trimegestone, levodesogestrel, gestodyne and nesterone.

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In one preferred embodiment, the tablet comprises estrogen in the form of ethinyl estradiol in an amount of about 10 micrograms to about 75 micrograms. In another preferred

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palatable. The primary ingredient of a carrier is one or more diluents. Non-limiting examples of diluents that can be used in accordance with this invention include microcrystalline cellulose, corn starch, modified starch, calcium carbonate, dicalcium phosphate, and poly-alcohol sugars such as dextrose, mannitol, sorbitol, xylitol, lactose, sucrose, and fructose. Many other diluents or other ingredients suitable as

(...)

The chewable tablet generally is not coated with a film or sugar coating. However, thin tablet coatings of a type known to those skilled in making coated tablets can be used.

- 3.1.13. La patente europea EP 1380301 publicada el 14 de Enero de 2004 y titulada "PHARMACEUTICAL COMBINATION OF ETHINYL ESTRADIOL AND DROSPIRENONE FOR USE AS A CONTRACEPTIVE" (equivalente a la WO 01/15701 A1 de marzo 8 de 2001), revela:

[0001] The present invention relates to a pharmaceutical composition comprising drospirenone and ethinylestradiol, a method of providing dissolution of drospirenone, methods of inhibiting ovulation by administration of drospirenone and the use of drospirenone and ethinylestradiol for inhibiting ovulation.

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[0010] Accordingly, in a first aspect, the present invention relates to a pharmaceutical composition comprising, as a first active agent, 6 β ,7 β ,15 β ,16 β -dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone (drospirenone) in an amount corresponding to a daily dosage, on administration of the composition, of from about 2 mg to about 4 mg, and, as a second active agent, 17 α -ethinylestradiol (ethinylestradiol) in an amount corresponding to a daily dosage of from about 0.01 mg to about 0.05 mg, together with one or more pharmaceutically acceptable carriers or excipients.

(...)

[0016] It has surprisingly been found that when drospirenone is provided in micronized form (so that particles of the active substance have a surface area of more than 10,000 cm²/g, and the following particle size distribution as determined under the microscope: not more

(...)

Examples of suitable excipients include fillers, e.g. sugars such as lactose, glucose or sucrose, sugar alcohols such as mannitol, sorbitol or xylitol, starch such as wheat, corn or potato starch, modified starch or sodium starch glycolate, lubricants such as talc, magnesium stearate, calcium stearate, colloidal silica or stearic acid, and binders such as polyvinylpyrrolidone, cellulose derivatives, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose or gelatin, for making oral dosage forms such as tablets, pills or capsules.

(...)

Además reivindica:

1. A pharmaceutical composition comprising, as a first active agent drospirenone in an amount corresponding to a daily dosage, on administration of the composition, of from about 2 mg to 4 mg, and as a second active agent, ethinylestradiol in an amount corresponding to a daily dosage of from about 0.01 mg to 0.05 mg, together with one or more pharmaceutically acceptable carriers or excipients, wherein said drospirenone has a surface area of more than 10 000 cm²/g.

Los documentos anteriores permiten demostrar que específicamente la combinación entre drospirenona y etinil estradiol en formulaciones anticonceptivas para administración oral tipo tableta, así como el uso de cantidades de dichos fármacos en rangos que incluyen los mencionados por la solicitud colombiana en

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trámite, en especial en las reivindicaciones 1, 3, 7, 8, 10, 12, 13, 14, 28, 42 y 43, pertenece al estado del arte por obra de la anterioridad citada y se podría decir que carece por completo de novedad y nivel inventivo, puesto que las mencionadas anterioridades ya revelaban la misma composición conformada por un progestágeno como Drospirenona y un estrógeno como Etinilestradiol en rangos similares a los que se pretende patentar en la solicitud que nos ocupa, pues para el caso de la Drospirenona está presente en un rango comprendido entre 2 y 4mg, al paso que en la solicitud en trámite una dosis preferida del mismo principio activo está entre 30,5 y 5mg, preferiblemente entre 2 y 4 mg, más preferiblemente 3mg, evidentemente comprendido en el rango anterior; y en cuanto a Etinil estradiol éste se encuentra en un rango entre 0,01mg y 0,05mg (10 a 50µg), al paso que la solicitud en trámite una dosis preferida de este mismo activo está entre 20 y 50µg, más preferiblemente entre 20 y 40µg y más preferiblemente 30µg.

Respecto de las dosis mencionadas, hago notar que la eventual concesión de la solicitud con base en las cantidades de los compuestos "Etinilestradiol" y "Drospirenona" empleados en la formulación, además de versar sobre un tratamiento terapéutico basado en la administración simultánea de dos principios activos para tratar una patología determinada –asunto expresamente prohibido por la norma andina-, supondría restringir injustificadamente a los médicos y desarrolladores de medicamentos la posibilidad de proponer y utilizar formulaciones de **etinilestradiol** con una dosis diaria en el rango desde aproximadamente 0.01mg hasta 0.05mg y de **Drospirenona** con una dosis diaria en el rango desde 2mg hasta 4mg.

3.2. Ahora bien, si el fundamento de novedad de la solicitud colombiana en trámite está dado por la presencia de Drospirenona NO micronizada tal como lo revelan las reivindicaciones 1, 2 y 5, es del caso citar que tan solo un documento en el estado del arte mencionan que Drospirenona puede encontrarse en forma micronizada, ellos son:

* La patente europea EP 1380301 de título "PHARMACEUTICAL COMBINATION OF ETHINYL ESTRADIOL AND DROSPIRENONE FOR USE AS A CONTRACEPTIVE" (equivalente a la solicitud internacional WO 01/15701 A1), mencionada en el numeral 3.1.13., en donde se revela que:

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[0016] It has surprisingly been found that when dros-
pirenone is provided in micronized form (so that parti-
cles of the active substance have a surface area of more
than 10,000 cm²/g, and the following particle size distri-
bution as determined under the microscope: not more
than 2 particles in a given batch with a diameter of more
than 30 μm, and preferably ≤ 20 particles with a diameter
of ≥ 10 μm and ≤ 30 μm) in a pharmaceutical composi-

Lo anterior nos lleva a pensar que, el resto de documentos pertenecientes al arte y patentes aquí citadas se refieren a Drospirenona NO micronizada, puesto que no se hace ninguna aclaración o especificación en cuanto al tipo, clase y características de la materia prima empleada.

Si tenemos en cuenta lo consignado en la solicitud internacional WO/01/15701: *cuando la Drospirenona está en forma micronizada, las partículas de la sustancia activa tienen un área superficial de más de 10,000cm²/g...* (cursiva fuera del texto), y lo revelado en las reivindicación 2 de la solicitud colombiana en trámite: *Drospirenona con un área superficial menor a 10,000cm²/g* (cursiva fuera del texto), es importante llamar la atención de este despacho en cuanto a que si bien es cierto no coinciden los valores relacionados con el área superficial en uno y otro documento, no lo es menos que, para cualquier persona medianamente versada en la materia y teniendo en cuenta que en el estado del arte se encuentra un documento que revela un área superficial superior a 10,000cm²/g, sería obvio darse a la tarea de proponer un rango menor a 10,000cm²/g para evitar infracciones de derechos de patentes; adicional a esto, si tenemos en cuenta que el área superficial para que las partículas se encuentren micronizadas es mayor a 10,000cm²/g (según la WO 01/15701), queda claro que cualquier valor que se encuentre por debajo del propuesto permitiría la obtención de partículas NO MICRONIZADAS como las pretendidas en la solicitud en trámite; en consecuencia, la caracterización hecha de la solicitud en función del área superficial y de si la drospirenona es o no micronizada carece al menos de nivel inventivo por obra de lo revelado en los documentos antes mencionados.

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Ahora bien, si tenemos en cuenta que el tamaño de partícula⁸ afecta la solubilidad puesto que influye en la superficie de la partícula y, por lo tanto y según la ecuación de Noyers-Whitney, puede aumentar la velocidad de disolución y que al disminuir el tamaño de partícula (por ejemplo al micronizar un principio activo), aumenta la superficie específica y la velocidad de disolución; entonces es lógico que una persona medianamente versada en la materia busque mejorar por otras vías (excipientes, vehículos, coeficiente de solubilidad, cristalinidad) la solubilidad de un principio activo que tiene un tamaño de partícula mayor al de una sustancia micronizada como es el caso que nos ocupa.

Es así que, en la solicitud colombiana en trámite se plantea la inclusión de un tensioactivo no-iónico para mejorar la humectación del fármaco, aumentar la solubilidad y la estabilidad de la composición; teniendo en cuenta esto, es preciso recordar que en el estado del arte y en la industria farmacéutica es bien sabido que los excipientes que se utilizan en la elaboración de una determinada formulación puede influir en las propiedades de solubilidad del principio activo y por lo tanto en las características de absorción y biodisponibilidad; por tal razón, es tan importante y tan habitual que en los estudios de preformulación sea necesario estudiar las características de velocidad de disolución del principio activo solo y en combinación con los distintos excipientes a través de pruebas *in Vitro* que se encuentran plasmadas y estandarizadas en las farmacopeas.

Dentro de la clasificación más común de los **tensioactivos** se encuentran los tensioactivos no-iónicos, los cuales son ampliamente conocidos y en su gran mayoría son ácidos grasos de cadena larga entre los cuales se encuentran los siguientes:

- los alcoholes grasos: como lauril, cetil y estearil alcoholes;
- los ésteres de glicerol: como mono, di y triglicéridos;
- los ésteres de ácidos grasos de alcoholes grasos y;
- otros alcoholes como propilenglicol, polietilenglicol, **sorbitan**, sucrosa, y colesterol.

Los surfactantes derivados de Sorbitan o mejor conocidos como Tween son ésteres del polioxietilen sorbitan parcialmente esterificados con ácidos grasos superiores, son agentes emulgentes del tipo surfactante no iónico que se emplean

⁸ En "Tecnología Farmacéutica", Vol 1: Aspectos fundamentales de los sistemas farmacéuticos y operaciones básicas; Cap 1 pag 37. Editorial Síntesis S.A; mayo 2001.

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como agentes dispersantes/suspensores, proporcionan emulsiones de fase externa acuosa, estables y de textura fina, también se usan como solubilizantes de una gran variedad de sustancias, como humectantes en la formulación de suspensiones orales y parenterales; entre los más representativos y conocidos en la literatura científica farmacéutica⁹ se encuentran los revelados en las reivindicaciones 16 a 21 de la solicitud colombiana en trámite y que corresponden a:

- * Polioxietilen-20 sorbitan monolaurato: Polisorbato 20 ó Tween-20®
- * Polioxietilen-20 sorbitan monoestearato: Polisorbato 60 ó Tween-60®,
- * Polioxietilen-20 sorbitan monooleato: Polisorbato-80 ó Tween-80®.

Lo anterior permitiría afirmar que el (los) surfactante(s) o tensioactivo(s) no iónico(s) que intervienen en la formulación, se comportarían como materiales que ayudan a la humectación y a la solubilidad; ésta es la razón por la cual, es obvio para un formulador el suponer la posibilidad de obtener una formulación de características mejoradas, su empleo no supone un asombroso aporte técnico, ya que una persona medianamente versada en la materia técnica, conociendo las características y propiedades de los principios activos, conociendo la función que cumplen los surfactantes mencionados y los otros excipientes dentro de una formulación, derivaría efectivamente, tras la etapa de preformulación, una composición que incluya el mismo principio activo y excipientes de la misma clase y aplicación farmacotécnica.

Por todo lo expuesto respetuosamente llamo la atención nuevamente sobre el hecho de que la solicitud de la referencia no cumple con los requisitos dispuestos en la Decisión 486 de 2000 y que por tal razón no puede ser objeto de privilegio de patente de invención.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, artículos 14, 16 y 18 (Requisitos de Patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

⁹ Arthur H. Kibbe. "Handbook of Pharmaceutical Excipients". Third Edition. 2000 American Pharmaceutical Association and Pharmaceutical Press. pp 416 a 419.

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V. SOLICITUD DE PLAZO EXTRA PARA SUSTENTAR LA OPOSICIÓN

En desarrollo de lo dispuesto por el artículo 42, inciso 2º de la Decisión 486, solicito comedidamente a su Despacho el plazo adicional de sesenta días para sustentar la presente oposición. Para los anteriores efectos, me permito anexar la constancia de pago correspondiente.

VI PRUEBAS

Ruego que se tenga como tal, sin perjuicio de las que puedan presentarse al vencimiento de la prórroga solicitada, y de aquellas que el Despacho considere oficiosamente, las siguientes:

- La publicación científica "An open-label, multicenter study to evaluate Yasmin, a low-dose combination oral contraceptive containing drospirenone, a new progestogen"
- La publicación científica "Drospirenone: pharmacology and pharmacokinetics of a unique progestogen"
- La publicación científica "Effect of a combined oral contraceptive containing 3 mg of drospirenone and 30 microg of ethinyl estradiol on the human endometrium"
- La publicación científica "New Monophasic Oral Contraceptive Containing Drospirenone Decreases Premenstrual Symptoms"
- La publicación científica "A comparative study of monophasic oral contraceptives containing either drospirenone 3 mg or levonorgestrel 150 µg on premenstrual symptoms"
- La publicación científica "Evaluation of a Unique Oral Contraceptive in the Treatment of Premenstrual Dysphoric Disorder"
- La publicación científica "Eficacia y Tolerancia de un Anticonceptivo Monofásico Oral con Estradiol y Drospirenona"
- La publicación internacional WO 98/04268 publicada el 05 de Febrero de 1998 y titulada "ORAL CONTRACEPTIVE" paginas 7, 8, 9, 12, 13, y capítulo reivindicatorio.

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- La publicación internacional WO 99/13882 publicada el 25 de Marzo de 1999 y titulada "ORAL CONTRACEPTIVE PREPARATION HAVING A FIRST PHASE PROGESTIN/ESTROGEN AND A SECOND PHASE COMPRISING PROGESTIN" paginas 5, 6, 7, 8 y capítulo reivindicatorio.
- La patente americana US 6,451,778 publicada el 17 de Septiembre de 2002 y titulada "ORLA CONTRACEPTIVE" columnas 6 y 7.
- La publicación internacional WO 02/094281 publicada el 28 de Noviembre de 2002 y titulada "MEANS AND METHOD FOR HORMONAL CONTRACEPTION" paginas 6, 9, 10, 11, 12 y capítulo reivindicatorio.
- La patente americana US 6,667,050 publicada el 23 de Diciembre de 2003 y titulada "CHEWABLE ORAL CONTRACEPTIVE" columnas 2, 3, 4, 5, 7 y capítulo reivindicatorio.
- La patente europea EP 1380301 publicada el 14 de Enero de 2004 y titulada "PHARMACEUTICAL COMBINATION OF ETHINYL ESTRADIOL AND DROSPIRENONE FOR USE AS A CONTRACEPTIVE" paginas 2, 3 y capítulo reivindicatorio.

VII. ANEXOS

Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos

1. Certificado de existencia y representación legal de Lafrancol S.A.
2. Poder para actuar.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Constancia de pago para sustentar la solicitud de prórroga a que se refiere el artículo 42, inciso 2º de la Decisión 486.
5. Copia para correr traslado al solicitante.
6. El mencionado en el acápite de pruebas.

VIII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 205, Fax (1) 621.25.42 de esta ciudad. Lafrancol S.A. las recibirá en sus oficinas localizadas en la Carrera 1 N° 46-84 de Cali.

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experience (Westhoff et al., 1994). Our results do not support the hypothesis that the number of IUDs inserted in residency is associated with current reported use of the IUD in clinical practice. Rather, the association of a respondent's conservative-to-liberal score in patient selection with IUD use may indicate that the teaching of candidate selection drives physicians' future use of the IUD."

"Our findings...have important implications for physician training and education," the researchers noted. "Because most obstetrician-gynecologists are inserting few IUDs, educational programs should target these physicians to expand their IUD use. Such programs should highlight the evidence for IUD safety and the rarity of litigation. The number of IUDs inserted in residency may be less important than the development of less conservative, evidence-based criteria for selecting IUD candidates."

"Many women could safely use the IUD but are not offered this contraceptive method because physicians' selection of IUD candidates is unduly restrictive," concluded Stanwood et al.

"Educating physicians about the safety of IUDs may expand their use of IUDs. More women would then be offered a method of convenient, safe, and highly effective long-term contraception."

The corresponding author for this study is Nancy L. Stanwood, MD, MPH, Department of Obstetrics and Gynecology, University of Rochester Medical Center, Box 669, Room 2-4446, 601 Elmwood Avenue, Rochester, NY 14642-8668.

Oral Contraception

New Monophasic Oral Contraceptive Containing Drospirenone Decreases Premenstrual Symptoms

An oral contraceptive containing drospirenone (DRSP) in combination with ethinyl estradiol (EE) may be more effective in reducing premenstrual symptoms than other combined OCs, according to researchers in this multicenter report.

"An oral contraceptive containing drospirenone/ethinyl estradiol may reduce the premenstrual symptoms of negative affect, water retention and increased appetite," wrote Candace Brown and colleagues ("A New Monophasic Oral Contraceptive Containing Drospirenone: Effect on Premenstrual Symptoms," *The Journal of Reproductive Medicine*, January 2002;47(1):14-22).

Five to ten percent of women report premenstrual symptoms that impact daily lifestyle (Logue and Moos, 1986; Moline, 1993; Daugherty, 1998). These symptoms tend to fall under several clusters, including negative affect, water retention, and impaired concentration. While some women receiving combined hormonal OCs may experience fewer cyclic symptoms than normally cycling (Moline, 1993; Woods et al., 1982; Moos, 1991), some symptoms, particularly those associated with water retention and mood swings, may increase with the use of some OCs (Bancroft and Rennie, 1993; Mortola, 1994).

An OC containing DRSP, 3 mg, in combination with EE, 30 µg, has been developed. "DRSP possesses direct antiandrogenic activity due to competitive binding to the androgen receptor," wrote Brown et al. "This androgen antagonist effect is in addition to the more indirect antiandrogenic properties of other progestogens; DRSP suppresses androgen production from the adrenals and ovaries (Muhn et al., 1995; Fuhrmann et al., 1996; Krattenmacher, 2000). Since increased levels of free testosterone positively correlate with premenstrual irritability, (Dougherty et al., 1997; Ericksson et al., 1992), the 'dual' antiandrogenic activity of DRSP may possess mood-stabilizing properties."

The authors sought to determine whether a new monophasic oral contraceptive containing DRSP/EE reduces premenstrual symptoms. "Based on the antimineralocorticoid and antiandrogenic properties of DRSP, it was hypothesized that an OC containing DRSP, 3 mg, in combination with EE, 30 µg might improve some of the physical and psychological symptoms associated with the perimenstruum," wrote Brown et al.

Three hundred and twenty-six healthy women aged 18-35 years participated in this open-label study conducted from December 1996 through July 1998 at six sites in the United States. Intrasubject changes in premenstrual symptoms were measured and compared between women who were new users of oral contraceptives and those who switched from previous contraceptives.

Atrás

1 página o páginas que se imprimirán.

Registro: 1

- Título:** An open-label, multicenter study to evaluate Yasmin, a low-dose combination oral contraceptive containing drospirenone, a new progestogen.
- Autor(es):** Parsey KS; Pong A
- Author's Address:** Berlex Laboratories, Montville, New Jersey 07045-1000, USA.
- Fuente:** Contraception [Contraception] 2000 Feb; Vol. 61 (2), pp. 105-11.
- Tipo de publicación:** Journal Article; Multicenter Study
- Idioma:** English
- Journal Information:** *Country of Publication:* UNITED STATES *NLM ID:* 0234361 *Publication Model:* Print *Cited Medium:* Print *ISSN:* 0010-7824 (Print) *Subsets:* MEDLINE
- Términos MeSH:** Aldosterone Antagonists/*standards
Androstenes/*standards
Contraceptives, Oral, Combined/*standards
Contraceptives, Oral, Hormonal/*standards
Progesterone Congeners/*standards
Adolescent; Adult; Aldosterone Antagonists/adverse effects; Aldosterone Antagonists/therapeutic use; Androstenes/adverse effects; Androstenes/therapeutic use; Blood Pressure; Body Weight; Contraceptives, Oral, Combined/adverse effects; Contraceptives, Oral, Combined/therapeutic use; Contraceptives, Oral, Hormonal/adverse effects; Contraceptives, Oral, Hormonal/therapeutic use; Ethinyl Estradiol/adverse effects; Ethinyl Estradiol/standards; Ethinyl Estradiol/therapeutic use; Female; Humans; Lipids/blood; Menstruation Disturbances/chemically induced; Patient Compliance; Progesterone Congeners/adverse effects; Progesterone Congeners/therapeutic use; Questionnaires; Uterine Hemorrhage/chemically induced
- Resumen:** This open-label, multicenter study evaluated the efficacy, safety, and cycle control of Yasmin, a new low-dose, monophasic oral contraceptive containing the unique progestogen drospirenone (DRSP) 3 mg and ethinyl estradiol (EE) 30 microg. DRSP is a synthetic progestogen that has antiandrogenic and antimineralocorticoid effects. In this study, 326 women were evaluated and 220 (67%) completed all 13 treatment cycles. The corrected Pearl Index was 0.407. Of the 151 subjects who experienced intermenstrual bleeding at any time during the study, the majority (64%) had bleeding during only one or two pill cycles. Breakthrough bleeding without spotting occurred in 1% of all cycles, spotting without breakthrough bleeding in 9.3% of all cycles, and breakthrough bleeding with spotting in 3% of all cycles. Amenorrhea was observed in 3% of all cycles. In all, 20 subjects (6%) discontinued participation in the study because of adverse events. No serious adverse events related to the study drug were reported. No clinically significant changes in weight, blood pressure, or lipids were reported. The impact of the new progestogen DRSP on the women's self-perception of menstrual health was also evaluated. Subjects reported that symptoms of water retention, negative affect, and increased appetite significantly improved at cycle 6 from baseline. This study demonstrates that Yasmin is an effective oral contraceptive that is safe and well tolerated.

Índice aportado:

Indexing Agency: PIP Local ID #: 149905. *Indexing Agency:* POP Local ID #: 00295508.

Keywords: Americas; Clinical Research; Clinical Trials*; Contraception; Contraceptive Agents; Contraceptive Agents, Female; Contraceptive Agents, Progestin*; Contraceptive Effectiveness*; Contraceptive Methods; Contraceptive Usage; Developed Countries; Family Planning; Health; Method Acceptability*; North America; Northern America; Oral Contraceptives; Oral Contraceptives, Combined*; Oral Contraceptives, Low-dose*; Public Health; Research Methodology; Research Report*; Safety*; United States

Note: TJ: CONTRACEPTION.

CAS Registry Number: 0 (Aldosterone Antagonists)

0 (Androstenes)

0 (Contraceptives, Oral, Combined)

0 (Contraceptives, Oral, Hormonal)

0 (Lipids)

0 (Progesterone Congeners)

57-63-6 (Ethinyl Estradiol)

67392-87-4 (drospirenone)

Fecha(s) de la entrada:

Date Created: 20000608 *Date Completed:* 20000608 *Latest Revision:* 20060518

Código de actualización:

20061223

PMID:

10802275

Base de datos:

MEDLINE

[Atrás](#)

Atrás

1 página o páginas que se imprimirán.

Registro: 1

- Título:** Drospirenone: pharmacology and pharmacokinetics of a unique progestogen.
- Autor(es):** Krattenmacher R
- Author's Address:** Berlex Laboratories, 300 Fairfield Road, 07470, Wayne, NJ, USA.
rolf_krattenmacher@berlex.com
- Fuente:** Contraception [Contraception] 2000 Jul; Vol. 62 (1), pp. 29-38.
- Tipo de publicación:** Journal Article; Review
- Idioma:** English
- Journal Information:** *Country of Publication:* UNITED STATES *NLM ID:* 0234361 *Publication Model:* Print *Cited Medium:* Print *ISSN:* 0010-7824 (Print) *Subsets:* MEDLINE
- Términos MeSH:** Androstenes/*pharmacology
Progesterone Congeners/*pharmacology
Androstenes/pharmacokinetics; Androstenes/therapeutic use; Animals; Contraceptive Agents, Female; Female; Humans; Menstruation/drug effects; Menstruation/physiology; Menstruation Disturbances/drug therapy; Progesterone/physiology; Progesterone Congeners/pharmacokinetics; Progesterone Congeners/therapeutic use; Receptors, Androgen/drug effects; Receptors, Androgen/physiology; Receptors, Steroid/drug effects; Receptors, Steroid/physiology; Renin-Angiotensin System/drug effects; Testosterone/metabolism
- Resumen:** The pharmacology and pharmacokinetics of drospirenone, a unique progestogen, are reviewed in this paper. Unlike other progestogens, drospirenone, an analogue of spironolactone, has biochemical and pharmacologic profiles similar to endogenous progesterone, especially regarding antimineralocorticoid and antiandrogenic activities. Drospirenone counteracts the estrogen-induced stimulation of the renin-angiotensin-aldosterone system and blocks testosterone from binding to androgen receptors. Because of these characteristics, it has the potential to reduce body weight, blood pressure, and low-density lipoprotein levels and to enhance high-density lipoprotein levels. As a combination oral contraceptive, drospirenone with ethinyl estradiol is effective and has positive effects on weight and lipid levels. Additionally, it relieves menstrually related symptoms (e.g., negative affect and water retention) that are commonly observed with other combination oral contraceptives. Based on the biochemical and pharmacodynamic data, drospirenone appears to be a viable alternative to the currently available progestogens.
- Número de referencias:** 27
- CAS Registry Number:** 0 (Androstenes)
0 (Contraceptive Agents, Female)
0 (Progesterone Congeners)
0 (Receptors, Androgen)
0 (Receptors, Steroid)
57-83-0 (Progesterone)
58-22-0 (Testosterone)

Atrás

1 página o páginas que se imprimirán.

Registro: 1

- Título:** Effect of a combined oral contraceptive containing 3 mg of drospirenone and 30 microg of ethinyl estradiol on the human endometrium.
- Autor(es):** Lüdiche F; Johannisson E; Helmerhorst FM; Campana A; Foidart J; Heithecker R
- Author's Address:** Department of Obstetrics and Gynecology, University Hospital Geneva, Geneva, Switzerland.
- Fuente:** Fertility And Sterility [Fertil Steril] 2001 Jul; Vol. 76 (1), pp. 102-7.
- Tipo de publicación:** Journal Article; Multicenter Study; Research Support, Non-U.S. Gov't
- Idioma:** English
- Journal Information:** *Country of Publication:* United States *NLM ID:* 0372772 *Publication Model:* Print *Cited Medium:* Print *ISSN:* 0015-0282 (Print) *NLM ISO Abbreviation:* Fertil. Steril. *Subsets:* MEDLINE
- Términos MeSH:** Androstenes/*pharmacology
Contraceptives, Oral/*pharmacology
Endometrium/*drug effects
Estradiol Congeners/*pharmacology
Ethinyl Estradiol/*pharmacology
Progesterone Congeners/*pharmacology
Adult; Androstenes/adverse effects; Atrophy; Cell Division/drug effects; Contraceptives, Oral/adverse effects; Drug Combinations; Endometrium/pathology; Endometrium/ultrasonography; Estradiol Congeners/adverse effects; Ethinyl Estradiol/adverse effects; Female; Humans; Progesterone Congeners/adverse effects
- Resumen:** **OBJECTIVE:** To provide an in-depth assessment of the effects of the combined oral contraceptive containing 30 microg of ethinyl estradiol and 3 mg of drospirenone (Yasmin, Schering AG, Berlin) on the endometrium by means of endometrial morphometry in comparison to an untreated cycle. **DESIGN:** The open, multicenter study consisted of one untreated precycle and 13 treatment cycles. **SETTING:** Four gynecologic clinics in Belgium, The Netherlands, and Switzerland were involved. **PATIENT(S):** Forty women with a history of regular menstrual cycles. **INTERVENTION(S):** Before the commencement of the trial, 3 months without any hormonal intake was obligatory. The first endometrial sample was done in the untreated precycle, adjusted to the day of LH peak plus 5 to 6 days. During the medication phase, endometrial samples were taken at cycle 3, 6 and 13. **MAIN OUTCOME MEASURE(S):** Primary outcome measure of the study was the morphologic assessment of the endometrium with measures such as glandular diameter, glandular epithelial height, and number of vacuolated cells per 1,000 glandular cells. Furthermore, the endometrial thickness was measured by ultrasound. **RESULT(S):** After 13 cycles of medication use the endometrium had an atrophic appearance in 63% of the subjects. The size of the glands, the glandular epithelial height, and the number of glands per square millimeter were already significantly reduced after 3 months' use. Histological and ultrasonographical evaluation of the endometrium indicated a suppression of the proliferative activity of the endometrium. **CONCLUSION (S):** The combination of 30 microg of ethinyl estradiol with 3 mg of drospirenone induces changes of the endometrium that are comparable with other combined oral contraceptives and exhibits a marked antiproliferative effect on the endometrium. The medication was proven to be an effective oral contraceptive and revealed good cycle control characteristics.
- Comentarios:** Comment in: Fertil Steril. 2002 Jun;77(6):1308-9; author reply 1309-11. (PMID: 12057752)
- CAS Registry Number:** 0 (Androstenes)

Ethinyl estradiol (30 µg) and drospirenone (3 mg) were administered for 13 menstrual cycles to all participants. Subjects completed the 23-item Women's Health Assessment Questionnaire at baseline and at the end of the sixth cycle.

Two hundred and twenty (67%) women completed 13 cycles. The remaining 106 (33%) women did not complete the study because of adverse events ($n = 20$, 6%), lack of efficacy ($n = 1$, <1%), protocol deviations ($n = 18$, 6%), withdrawal of consent ($n = 26$, 8%), missing information ($n = 3$, <1%) or other reasons ($n = 38$, 12%). The most frequently reported adverse events leading to discontinuation were emotional lability, headache, nausea, dysmenorrhea, intermenstrual bleeding, and depression. All occurred at frequencies of <1.5%.

Of the 326 subjects in the parent study, 230 (71%) reported at least one adverse event during the study (Parsey and Pong, 2000). The most frequently reported adverse events (>5%) either possibly or probably related to the study drug were breast pain, reported by 28 women (8.6%), and headache, reported by 16 (4.9%). No serious adverse events related to the study drug were reported.

At the end of six weeks, premenstrual and menstrual symptom scores on the negative affect and water retention scales were reduced significantly relative to baseline, as was increased appetite during the premenstrual and menstrual phases. Improvements were similar among new users of hormonal contraceptives and those who switched from previous contraceptives.

Impaired concentration scores were not significantly reduced from baseline, and assessments of undesired hair changes and feelings of well-being did not change appreciably.

"The present study demonstrated that DRSP/EE consistently improved mood symptoms in a mildly symptomatic population," wrote Brown et al. "The most striking reductions in symptoms among all subjects, new users and switchers, occurred in irritability and mood swings during the premenstrual and menstrual phases."

"Because, in the present study, both new and previous users of OCs improved in water retention and affective symptoms over baseline, it is reasonable to expect that DRSP/EE may be more effective in reducing premenstrual symptoms than other combined OCs," wrote Brown et al. "However, a direct comparison in a placebo-controlled study is necessary to confirm this finding."

The corresponding author for this study is Candace Brown, Pharm.D., C.F.N.P., 9685 US Highway 70, Lakeland, TN 38002.

Transdermal Contraception

20-cm² Norelgestromin/Ethinyl Estradiol Patch is Safe and Effective

The transdermal contraceptive patch is a unique new method of combination hormonal contraception, according to researchers in this multicenter study. The results of this study demonstrate that contraceptive doses of estrogen and progestin can be delivered across the skin barrier.

"The 20-cm² patch (Ortho Evra) provided ovulation suppression, cycle control, and safety similar to that of Ortho-Cyclen, with significantly better compliance," wrote Richard Dittich and colleagues ("Transdermal Contraception: Evaluation of Three Transdermal Norelgestromin/Ethinyl Estradiol Doses in a Randomized, Multicenter, Dose-Response Study," *American Journal of Obstetrics and Gynecology*, January 2002; 186(1):15-20).

A new contraceptive patch (Ortho Evra/Evra), which may offer advantages over oral contraceptives (OCs), has been developed. The advantages of this patch include greater convenience (once-weekly dosing rather than daily dosing), better user compliance, dosing that is not affected by gastrointestinal disturbances, and the elimination of the daily peaks and troughs in progestin and estrogen serum levels seen with oral dosing. Unlike long-acting contraceptives, the patch is user-controlled and is readily reversible.

The authors sought to identify the dose for a contraceptive patch that provides a predetermined level of ovulation suppression and cycle control and is well tolerated. Additionally, the impact of a one-day delay in patch application or OC ingestion on suppression of ovulation was evaluated.

[Atrás](#)

1 página o páginas que se imprimirán.

Registro: 1

Título: A comparative study of monophasic oral contraceptives containing either drospirenone 3 mg or levonorgestrel 150 µg on premenstrual symptoms.

Autores: Sangthawan, Malinee msangthawan@hotmail.com
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**Author-Supplied
Keywords:** Drospirenone
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Premenstrual symptoms
Oral contraceptive

Resumen: Abstract: This open-label randomized study compared the effects of two combined oral contraceptives (OCs) containing 3 mg drospirenone (DRSP)/30 µg ethinyl estradiol (EE) with 150 µg levonorgestrel (LNG)/30 µg EE on the prevalence and changes from baseline of premenstrual symptoms after six cycles. The symptoms were measured using the Women's Health Assessment Questionnaire. Subjects receiving DRSP/EE had fewer prevalence of premenstrual symptoms than those receiving LNG/EE after six cycles. A significantly lower score of negative affect category in the premenstrual phase was demonstrated in those receiving DRSP/EE more than LNG/EE. The DRSP/EE group showed a greater improvement of mean scores from baseline in the premenstrual phase compared with those who received LNG/EE on negative affect as seen in the items on anxiety, irritability, feeling sad or blue and weight gain in the category of water retention. In conclusion, OCs containing DRSP have beneficial effects in reducing the prevalence of premenstrual symptoms especially the symptoms of negative affect and weight gain, particularly when compared to LNG/EE. Hence, it should be recommended for women who are susceptible to these adverse symptoms. [Copyright 2005 Elsevier]

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[Atrás](#)

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Evaluation of a Unique Oral Contraceptive in the Treatment of Premenstrual Dysphoric Disorder

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ABSTRACT

Premenstrual dysphoric disorder (PMDD) is a severe form of premenstrual syndrome (PMS). This is the first trial of a unique oral contraceptive containing a combination of drospirenone (DRSP, 3 mg) and ethinyl estradiol (EE, 30 μ g) for the treatment of PMDD. DRSP is a spironolactone-like progestin with antiandrogenic and antimineralocorticoid activity. Spironolactone has been shown to be beneficial in PMS, whereas oral contraceptives have shown conflicting results. In this double-blind, placebo-controlled trial, 82 women with PMDD (*Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. [DSM IV]) were randomized to receive DRSP/EE or placebo for three treatment cycles. The primary end point was change from baseline in luteal phase symptom scores as assessed on the Calendar of Premenstrual Experiences (COPE) scale. Patients treated with DRSP/EE showed a numerically greater change from baseline compared with those treated with placebo on each of the 22 COPE items and each of the 4 symptom factors. Between-group differences in symptom improvement reached statistical significance in factor 3 only (appetite, acne, and food cravings, $p = 0.027$). The secondary end points, Beck Depression Inventory (BDI) and Profile of Mood States (PMS), were consistent with the primary end point in that patients treated with the oral contraceptive showed a numerically greater improvement from baseline compared with those treated with placebo. The results of this study show a consistent trend in the reduction of symptoms that suggested a beneficial effect of DRSP/EE for the treatment of PMDD, despite limitations of the study design.

INTRODUCTION

UP TO 80% OF WOMEN EXPERIENCE physical and emotional changes that are related to their menstrual cycle. Among the nearly 150 reported

cyclically recurrent emotional and somatic symptoms, the most common include irritability, fatigue, depression or mood swings, breast tenderness, bloating, and food cravings. In 5%–10% of women, these symptoms can become severe

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Eficacia y Tolerancia de un Anticonceptivo Monofásico Oral con Estradiol y Drospirenona

Huber J, Foidart J, Wuttke W y colaboradores

Departamento de Ginecología y Obstetricia de la Universidad de Liège, Bélgica

[Efficacy and Tolerability of a Monophasic Oral Contraceptive Containing Ethinylestradiol and Drospirenone]

The European Journal of Contraception and Reproductive Health Care

5(1):25-34, Mar 2000

La combinación de 30 µg de etinilestradiol y 3 mg de drospirenona provee una efectiva anticoncepción oral, excelente control del ciclo, buena tolerancia y disminución de peso corporal que mejora el cumplimiento del tratamiento.

Introducción

Actualmente se desarrollan nuevos anticonceptivos con el fin de mejorar la tolerancia sin disminución de la efectividad y manteniendo un buen control del ciclo. Al respecto, dicen los autores, dos son las vías de investigación: 1) mediante la disminución de la dosis de los dos componentes (estrógenos y progestágenos); y 2) a través de la utilización de nuevos progestágenos con un perfil farmacológico más favorable. Uno de estos nuevos gestágenos es la drospirenona (DRSP), que presenta características farmacológicas similares a las de la progesterona natural. No sólo se trata de un poderoso progestágeno, sino que también demuestra actividad antimineralocorticoide leve y antiandrogénica. Estas características le permitirían a un anticonceptivo con DRSP disminuir la retención hidrosalina propia de otros gestágenos sintéticos que se traduce en aumento de peso.

Se ha demostrado que 2 mg de DRSP inhiben efectivamente la ovulación, aunque para lograr un margen de seguridad clínica se prefiere una dosis de 3 mg/día.

El presente estudio, realizado a gran escala, comparó los perfiles farmacológicos de una preparación anticonceptiva conteniendo 30 µg de etinilestradiol (EE2) y 3 mg de DRSP con los de un anticonceptivo tradicional con 30 µg de EE2 y 150 µg de desogestrel. El objetivo primario de este trabajo fue evaluar el control del ciclo y secundariamente medir la eficacia anticonceptiva, la tolerancia y los efectos adversos.

Material y métodos

El estudio aleatorizado comprendió 80 centros de 8 países europeos, e incluyó 13 ciclos de tratamiento, con un período de seguimiento de 6 meses sobre un total de 2 069 mujeres. Las participantes fueron asignadas a dos grupos de tratamiento: el primero quedó conformado por 1 657 pacientes que recibieron la nueva preparación (grupo de casos), mientras que 412 fueron tratadas con el anticonceptivo tradicional (grupo control). Ambas preparaciones fueron administradas durante 21 días consecutivos, con un descanso posterior libre de medicación de 7 días. Todas las pacientes fueron evaluadas por un investigador durante los ciclos 2 o 3, 6, 9 y 13, y nuevamente 6 semanas después de finalizado el período de tratamiento.

Los criterios de inclusión comprendieron edad entre 18 y 35 años (hasta 30 años para las fumadoras), no utilización de otros preparados hormonales ni de otros anticonceptivos (salvo condones para protección contra las enfermedades de

transmisión sexual). Los criterios de exclusión fueron embarazo o lactancia, enfermedades hepáticas, vasculares, metabólicas, tumores, infecciones genitales, abuso de alcohol o drogas, uso de anticonceptivos parenterales de depósito en los meses previos y de preparados para el tratamiento del síndrome premenstrual o diuréticos.

Todas las participantes fueron sometidas a controles clínicos, bioquímicos y hematológicos. La eficacia anticonceptiva fue medida mediante el índice de Pearl; el control del ciclo fue evaluado según el patrón de sangrado registrado por la propia mujer. Se prestó especial atención a las manifestaciones cutáneas como acné o seborrea.

Resultados

De las 2 069 mujeres que recibieron tratamiento, sólo 1 615 completaron el estudio; y 469 completaron la fase de medicación pero no la de seguimiento. El anticonceptivo con drospirenona proveyó una efectividad anticonceptiva similar a la lograda con el que incluía desogestrel. Hubo en total 18 418 ciclos de tratamiento con la combinación EE2/DRSP, y 4 685 ciclos con el preparado de EE2/desogestrel (EE2/Des). Once mujeres quedaron embarazadas, 10 con EE2/DRSP y una con EE2/Des; de ellas, sólo un caso en el grupo EE2/DRSP fue considerado falla potencial del método. El índice de Pearl, corregido para el uso de condón, fue de 0.71 para EE2/DRSP. En 9 embarazos ocurridos con EE2/DRSP se identificaron cofactores (olvido de toma de grageas, diarrea, etc.) que habrían reducido la eficacia anticonceptiva. Por ello, el índice de Pearl, teniendo en cuenta el único caso de falla atribuible al método, fue de 0.07 para EE2/DRSP. En el grupo tratado con EE2/Des ocurrió un caso atribuible a falla del método, con un índice de Pearl de 0.28.

Control del ciclo

Tanto en el grupo EE2/DRSP como en el EE2/Des el control del ciclo fue bueno, señalan los autores, comprobándose una baja incidencia de sangrado intermenstrual en ambos, mayor en el primer ciclo y luego gradualmente decreciente en los ciclos subsiguientes. En ambos grupos la mayoría de las mujeres refirieron sangrados por privación que duraron entre 4 y 7 días.

En el grupo de EE2/DRSP, el 83.9% de las mujeres presentó un sangrado por privación de 4 a 7 días de duración en el primer ciclo, el 12.1% de 1 a 3 días, y el 2.8% de más de 7 días. Este patrón fue similar para el grupo de EE2/Des. La

duración promedio del sangrado en el grupo de EE2/DRSP descendió de 4.9 días en el ciclo 1 a 4.6 días en el ciclo 12, siendo estos valores de 5 y 4.6 días para el grupo de EE2/DRSP, respectivamente. Aproximadamente el 0.8% de los ciclos en ambos grupos se complicó con amenorrea; es decir, falta de sangrado por privación.

Peso corporal y tensión sanguínea

Se observó descenso ponderal respecto del peso medio al comienzo del tratamiento en ambos grupos en cada ciclo y durante el seguimiento; pero la pérdida media de peso fue significativamente mayor en el grupo de EE2/DRSP (-0.46 kg) que en el EE2/Des (-0.19 kg) ($p < 0.0072$). La tendencia al descenso ponderal máximo se observó hacia el octavo ciclo en ambos grupos; posteriormente, el peso se recuperó de manera gradual hasta alcanzar los valores basales hacia el final del tratamiento. El porcentaje de mujeres que aumentaron o perdieron más de 2 kg fue mucho mayor en el grupo de E/Dro en todos los ciclos. No se manifestaron cambios significativos con respecto a la tensión arterial en ninguno de los grupos.

Efectos adversos y acción sobre la piel

La incidencia de efectos no deseados fue similar en ambos grupos (38.5% para EE2/DRSP Vs. 32.3% para EE2/Des; N/S), los más comunes fueron cefaleas, mastalgia, náuseas, dolor abdominal y migraña. La incidencia de efectos adversos graves fue similar en ambos grupos y siempre muy baja. Los parámetros hematológicos permanecieron normales en ambos grupos durante todo el tratamiento.

La incidencia e intensidad del acné disminuyeron significativamente en ambos grupos; entre las tratadas con EE2/DRSP el descenso observado hacia el ciclo 13 fue de 21.5% a 7.8%, en tanto para aquellas que recibieron EE2/Des resultó de 20.1% a 8.2%. La disminución de la

incidencia de seborrea entre las tratadas con EE2/DRSP fue de 11.7% a 2.8% en el ciclo 13, y descendió de 11.9% a 2.5% entre las que recibieron EE2/Des.

Discusión

Las dos preparaciones estudiadas demostraron una buena eficacia anticonceptiva y control del ciclo, con buena tolerancia. Se observó una tendencia a un menor sangrado intermenstrual en el grupo de EE2/DRSP, con menor tasa de incidencia en 9 de los 13 ciclos del estudio. Sin embargo, agregan los autores, cuando se analizaron las tasas de sangrado intermenstrual entre los ciclos 2-6 y 2-13 no se hallaron diferencias significativas entre los grupos. Las bajas tasas de sangrado intermenstrual y de amenorrea son alentadoras, dado que se trata de aspectos muy preocupantes para las usuarias de anticonceptivos que generan innecesarias visitas al ginecólogo.

La tolerancia objetiva y subjetiva para ambas preparaciones resultó buena, y los efectos adversos referidos fueron los habituales para los anticonceptivos orales. La disminución de la seborrea y acné fue importante para ambos fármacos.

El aumento ponderal es una queja frecuente entre las usuarias de anticonceptivos orales y una importante razón para interrumpir su uso. Por tanto, señalan los expertos, un anticonceptivo que evite este problema disminuirá la tasa de abandono del método. Si bien la pérdida de peso ocurrió en ambos grupos, fue más rápida, marcada y duradera en el grupo de EE2/DRSP.

Los datos del estudio permiten concluir a sus autores que la combinación de 3 mg de DRSP con 30 µg de EE2 provee una efectiva protección anticonceptiva y buen control del ciclo, además de ser bien tolerada y de evitar el incremento de peso por retención hidrosalina. Este último punto es considerado importante por su potencial prevención del abandono del método anticonceptivo.

Resumen objetivo elaborado por el Comité de Redacción Científica de SIIC, en base al artículo original completo publicado por la fuente editorial.

PCT

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(21) International Application Number: PCT/US97/12786 (22) International Filing Date: 23 July 1997 (23.07.97) (30) Priority Data: 08/686,786 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.</i> <i>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: ORAL CONTRACEPTIVE		
(57) Abstract		
This invention provides a method of contraception which comprises administering to a female of child bearing age for 23-25 consecutive days, a first phase combination of a progestin at a daily dosage of 40-500 μg trimegestone, 250 μg - 4mg dienogest, or 250 μg - 4mg drospirenone, and an estrogen at a daily dosage equivalent in estrogenic activity to 10-20 μg ethinyl estradiol for 3-8 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 3-8 days, a second phase combination of a progestin at a daily dosage of 40-500 μg trimegestone, 250 μg - 4 mg dienogest, or 250 μg - 4 mg drospirenone, and an estrogen at a daily dosage equivalent in estrogenic activity to 10-20 μg ethinyl estradiol, for 4-15 days, beginning on the day immediately following the last day of administration of the first phase combination, wherein the same dosage of the progestin and estrogen combination is administered in each of the 4-15 days, and a third phase combination of a progestin at a daily dosage of 40-500 μg trimegestone, 250 μg - 4 mg dienogest, or 250 μg - 4 mg drospirenone, and an estrogen at a daily dosage equivalent in estrogenic activity to 10-20 μg ethinyl estradiol, for 4-15 days beginning on the day immediately following the last day of administration of the second phase combination, wherein the same dosage of the progestin and estrogen combination is administered in each of the 4-15 days provided that the daily dosage of the combination administered in the first phase is not the same as the daily dosage of the combination administered in the second phase and that the daily dosage of the combination administered in the second phase is not the same as the daily dosage of the combination administered in the third phase.		

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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.

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 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.

DESCRIPTION OF THE INVENTION

This invention provides a triphasic 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, the low dose progestin/estrogen combination is administered for 23-25-days per cycle according to a triphasic regimen that is described below. 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, so that the total administration period per cycle

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is 28 days per cycle to aid in compliance with the desired contraceptive regimen. Alternatively, the 3-5-day interval can be pill free.

More particularly, this invention provides a method of contraception which comprises administering to a female of child bearing age a first phase of 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 3-8 days beginning on day 1 of the menstrual cycle. The same daily dosage of the progestin and estrogen is administered for each of the 3-8 days. A second phase of 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 is administered for 4-15 days beginning on the day immediately following the last day of administration of the first phase. The same daily dosage of the progestin and estrogen is administered for each of the 4-15 days. A third phase of 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 at a daily dosage equivalent in estrogenic activity to 10-20 μ g ethinyl estradiol is administered for 4-15 days beginning on the day immediately following the last day of administration of the second phase. The same daily dosage of the progestin and estrogen is administered for each of the 4-15 days. The total administration for all three phases is 23-25 days. The daily dosage of the progestin/estrogen combination administered in any phase is distinct from the dosage of the progestin/estrogen combination administered in either of the other two phases.

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 3-5 days (through day 28 of the menstrual cycle) or the 3-5 days following administration of the contraceptive combination may be pill free.

It is preferred that total administration of the progestin/estrogen combination be 24 days. Preferred phase lengths are shown in the following table, with Phase Regimens A and B being most preferred for the triphasic rising regimens that are described below, and Phase Regimens E and F are most preferred for the triphasic midpeak regimens that are described below.

	<u>Phase Regimen</u>	<u>Phase 1 (days)</u>	<u>Phase 2 (days)</u>	<u>Phase 3 (days)</u>
5	A	7	7	10
	B	5	5	14
	C	5	8	11
	D	6	6	12
	E	7	10	7
	F	6	12	6
10	G	6	8	10
	H	4	8	12
	I	5	14	5
	J	6	10	8

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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. 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.

In one specific preferred embodiment of this invention termed a "triphasic rising regimen," the dosage of progestin is higher in the second phase than in the first phase and is higher in the third phase than in the second phase. With these regimens, the third phase will generally have the longest duration. In general, the estrogen dosage in the second phase is greater than the first phase, and the estrogen dosage in third phase is greater than the second phase; can rise from the first phase to the second phase, and then remain the same for the third phase; or can remain the same for all three phases.

The following daily dosages of a combination of trimegestone and ethinyl estradiol are preferred for contraception when administered according to a triphasic rising regimen for 23-25 consecutive days beginning on the first day of menses, with 24 days being preferred. The preferred phase lengths are provided above. Of the regimens provided below, Regimen B is more preferred. In the table below, trimegestone is abbreviated as TMG and ethinyl estradiol is abbreviated as EE.

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The following daily dosages of a combination of dienogest and ethinyl estradiol are preferred for contraception when administered according to a triphasic mid-peak regimen for 23-25 consecutive days beginning on the first day of menses, with 24 days being preferred. The preferred phase lengths are provided above. Of the regimens provided below, Regimen B is more preferred. In the table below, dienogest is abbreviated as DGST and ethinyl estradiol is abbreviated as EE.

PREFERRED DAILY DOSAGES

10	Regimen	Phase 1		Phase 2		Phase 3	
		DGST	EE	DGST	EE	DGST	EE
	A	750 µg	10 µg	2 mg	20 µg	1 mg	15 µg
	B	500 µg	10 µg	1 mg	20 µg	750 µg	15 µg
	C	750 µg	10 µg	2 mg	15 µg	1 mg	15 µg
	D	500 µg	10 µg	1 mg	15 µg	750 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 according to a triphasic mid-peak regimen for 23-25 consecutive days beginning on the first day of menses, with 24 days being preferred. The preferred phase lengths are provided above. Of the regimens provided below, Regimen C is more preferred. In the table below, drospirenone is abbreviated as DRSP and ethinyl estradiol is abbreviated as EE.

PREFERRED DAILY DOSAGES

25	Regimen	Phase 1		Phase 2		Phase 3	
		DRSP	EE	DRSP	EE	DRSP	EE
	A	2 mg	10 µg	4 mg	20 µg	3 mg	15 µg
	B	1 mg	10 µg	3 mg	20 µg	2 mg	15 µg
	C	500 µg	10 µg	2 mg	20 µg	1 mg	15 µg
	D	2 mg	10 µg	4 mg	15 µg	3 mg	15 µg
30	E	1 mg	10 µg	3 mg	15 µg	2 mg	15 µg
	F	500 µg	10 µg	2 mg	15 µg	1 mg	15 µg

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

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

This invention also provides a contraceptive kit adapted for daily oral
20 administration which comprises, 3-8 first phase dosage units each containing fixed dosage of a combination of a progestin at a daily dosage of 40-500 µg trimegestone, 250 µg - 4 mg dienogest, or 250 µg - 4 mg drospirenone, and an estrogen at a daily dosage equivalent in estrogenic activity to 10-20 µg ethinyl estradiol; 4-15 second phase dosage units each containing fixed dosage of a combination of a progestin at a daily
25 dosage of 40-500 µg trimegestone, 250 µg - 4 mg dienogest, or 250 µg - 4 mg drospirenone, and an estrogen at a daily dosage equivalent in estrogenic activity to 10-20 µg ethinyl estradiol, and 4-15 third phase dosage units each containing fixed dosage of a combination of a progestin at a daily dosage of 40-500 µg trimegestone, 250 µg - 4 mg dienogest, or 250 µg - 4 mg drospirenone, and an estrogen at a daily dosage
30 equivalent in estrogenic activity to 10-20 µg ethinyl estradiol, such that the total number of combination progestin/estrogen dosage units is 23-25. In another embodiment, the contraceptive kit contains 28 daily dosage units with 4 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
35 tablet dispenser. Specific referred progestins and estrogens and the specifically preferred dosages of each combination dosage unit are 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 for 23-25 consecutive days,
 - 5 a first phase combination of a progestin at a daily dosage selected from the group consisting of 440-500 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 3-8 days beginning on day 1 of the menstrual cycle, wherein the same dosage of the progestin and estrogen
10 combination is administered in each of the 3-8 days,
 - a second phase combination of a progestin at a daily dosage selected from the 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 4-15 days beginning on the day
15 immediately following the last day of administration of the first phase combination, wherein the same dosage of the progestin and estrogen combination is administered in each of the 4-15 days, and
 - a third phase combination of a progestin at a daily dosage selected from the 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 4-15 days beginning on the day
20 immediately following the last day of administration of the second phase combination, wherein the same dosage of the progestin and estrogen combination is administered in each of the 4-15 days
- 25 provided that the daily dosage of the combination administered in the first phase is not the same as the daily dosage of the combination administered in the second phase and that the daily dosage of the combination administered in the second phase is not the same as the daily dosage of the combination administered in the third phase.
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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.
- 35 3. The method according to claim 2, wherein the estrogen is ethinyl estradiol.

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4. The method according to claim 3, wherein the progestin of the first phase combination is administered at a daily dosage selected from the group consisting of 40-75 μ g trimegestone, 500-750 μ g dienogest, and 500 μ g - 2 mg drospirenone,
- 5 the progestin of the second phase combination is administered at a daily dosage selected from the group consisting of 50-125 μ g trimegestone, 750 μ g - 1 mg dienogest, and 1-3 mg drospirenone, and the progestin of the third phase combination is administered at a daily dosage selected from the group consisting of 75-250 μ g trimegestone, 1-2 mg dienogest, and 2-4 mg drospirenone.
- 10 2-4 mg drospirenone.
5. The method according to claim 4, wherein the total days of administration of the first phase combination plus the second phase combination plus the third phase combination is 24.
- 15 6. The method according to claim 5, wherein the first phase combination is administered for 7 days, the second phase combination is administered for 7 days, and the third phase combination is administered for 10 days.
- 20 7. The method according to claim 5, wherein the first phase combination is administered for 5 days, the second phase combination is administered for 5 days, and the third phase combination is administered for 14 days.
- 25 8. The method according to claim 5, wherein the daily dosage of trimegestone administered in the first phase combination is 50 μ g, the daily dosage of trimegestone administered in the second phase combination is 75 μ g, the daily dosage of trimegestone administered in the third phase combination is 125 μ g, the daily dosage of ethinyl estradiol administered in the first phase combination is 10 μ g, the daily dosage of ethinyl estradiol administered in the second phase combination is 15 μ g, and the daily dosage of ethinyl estradiol administered in the third phase combination is 20 μ g.
- 30 9. The method according to claim 5, wherein the daily dosage of dienogest administered in the first phase combination is 500 μ g, the daily dosage of dienogest administered in the second phase combination is 750 μ g, the daily dosage of dienogest administered in the third phase combination is 1 mg, the daily dosage of ethinyl estradiol administered in the first phase combination is 10 μ g, the daily dosage of
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ethinyl estradiol administered in the second phase combination is 15 μ g, and the daily dosage of ethinyl estradiol administered in the third phase combination is 20 μ g.

10. The method according to claim 5, wherein the daily dosage of drospirenone administered in the first phase combination is 1 mg, the daily dosage of drospirenone administered in the second phase combination is 2 mg, the daily dosage of drospirenone administered in the third phase combination is 3 mg, the daily dosage of ethinyl estradiol administered in the first phase combination is 10 μ g, the daily dosage of ethinyl estradiol administered in the second phase combination is 15 μ g, and the daily dosage of ethinyl estradiol administered in the third phase combination is 20 μ g.

11. The method according to claim 3, wherein the progestin of the first phase combination is administered at a daily dosage selected from the group consisting of 40-75 μ g trimegestone, 500-750 μ g dienogest, and 500 μ g - 2 mg drospirenone, the progestin of the second phase combination is administered at a daily dosage selected from the group consisting of 50-125 μ g trimegestone, 750 μ g - 1 mg dienogest, and 1-3 mg drospirenone, and the progestin of the third phase combination is administered at a daily dosage selected from the group consisting of 75-250 μ g trimegestone, 1-2 mg dienogest, and 2-4 mg drospirenone.

12. The method according to claim 11, wherein the total days of administration of the first phase combination plus the second phase combination plus the third phase combination is 24.

13. The method according to Claim 12, wherein the first phase combination is administered for 7 days, the second phase combination is administered for 10 days, and the third phase combination is administered for 7 days.

14. The method according to Claim 12, wherein the first phase combination is administered for 6 days, the second phase combination is administered for 12 days, and the third phase combination is administered for 6 days.

15. The method according to claim 12, wherein the daily dosage of trimegestone administered in the first phase combination is 50 μ g, the daily dosage of trimegestone administered in the second phase combination is 125 μ g, the daily dosage of

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trimegestone administered in the third phase combination is 75 μ g, the daily dosage of ethinyl estradiol administered in the first phase combination is 10 μ g, the daily dosage of ethinyl estradiol administered in the second phase combination is 20 μ g, and the daily dosage of ethinyl estradiol administered in the third phase combination is 15 μ g.

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16. The method according to claim 12, wherein the daily dosage of dienogest administered in the first phase combination is 500 μ g, the daily dosage of dienogest administered in the second phase combination is 1 mg, the daily dosage of dienogest administered in the third phase combination is 750 μ g, the daily dosage of ethinyl estradiol administered in the first phase combination is 10 μ g, the daily dosage of ethinyl estradiol administered in the second phase combination is 20 μ g, and the daily dosage of ethinyl estradiol administered in the third phase combination is 15 μ g.

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17. The method according to claim 12, wherein the daily dosage of drospirenone administered in the first phase combination is 500 μ g, the daily dosage of drospirenone administered in the second phase combination is 2 mg, the daily dosage of drospirenone administered in the third phase combination is 1 mg, the daily dosage of ethinyl estradiol administered in the first phase combination is 10 μ g, the daily dosage of ethinyl estradiol administered in the second phase combination is 20 μ g, and the daily dosage of ethinyl estradiol administered in the third phase combination is 15 μ g.

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18. 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 second phase combination, such that the total days of administration of the first phase combination plus the second phase combination plus the third phase combination plus the non-contraceptive placebo equals 28 days.

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19. The method according to claim 22 in which the non-contraceptive placebo contains an iron supplement.

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20. A three phase contraceptive kit adapted for daily oral administration which comprises;

3-8 first phase dosage units each containing a combination of a progestin at a daily dosage selected from the 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, provided

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that each of the dosage units contains the same dosage of progestin and estrogen;

5 4-15 second phase dosage units each containing 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, provided that each of the dosage units contains the same dosage of progestin and estrogen, and

10 4-15 third phase dosage units each containing 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, provided that each of the dosage units contains the same dosage of progestin and estrogen,

15 and provided that the daily dosage of the first phase dosage units are not the same as the daily dosage of the second phase dosage units, and that the daily dosage of the second phase dosage units are not the same as the daily dosage of the third phase dosage units,

20 such that the total number of dosage units in the kit equals 23-25.

21. The contraceptive kit according to claim 20 wherein the estrogen is the same for all three phases and is selected from the group consisting of ethinyl estradiol; 17 β -estradiol; conjugated estrogens, USP; estrone or a salt thereof; and mestranol.

25 22. The contraceptive kit according to claim 21, wherein the total number of dosage units equals 24.

23. A contraceptive kit adapted for daily oral administration which comprises;

30 3-8 first phase dosage units each containing 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, provided that each of the dosage units contains the same dosage of progestin and estrogen;

35 4-15 second phase dosage units each containing 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

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dosage equivalent in estrogenic activity to 10-20 μg ethinyl estradiol, provided that each of the dosage units contains the same dosage of progestin and estrogen,

- 5 4-15 third phase dosage units each containing 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, provided that each of the dosage units contains the same dosage of progestin and estrogen, and
- 10 3-5 dosage units each containing a non-contraceptive placebo, provided that the daily dosage of the first phase dosage units are not the same as the daily dosage of the second phase dosage units, and that the daily dosage of the second phase dosage units are not the same as the daily dosage of the third phase dosage units,
- 15 such that the total number of dosage units in the kit equals 28.

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(54) Title: ORAL CONTRACEPTIVE PREPARATION HAVING A FIRST PHASE COMPRISING PROGESTIN/ESTROGEN AND A SECOND PHASE COMPRISING PROGESTIN			
(57) Abstract This invention provides a method of contraception which comprises administering to a female of child bearing age for 28 days per menstrual cycle a combination of a progestin at a daily dosage equivalent to 30-150 µg levonorgestrel and an estrogen at a daily dosage equivalent to 10-20 µg ethinyl estradiol for 23-25 days beginning on day 1 of the menstrual cycle, followed by administering a progestin at a daily dosage equivalent to 10-100 µg levonorgestrel for 3-5 days.			

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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.

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.

DESCRIPTION OF THE INVENTION

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This invention provides a progestin bridged 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 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 a progestin 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 23-25-day administration period, a progestin is administered for 3-5 days to assist in maintaining good cycle control. The total administration during each cycle is 28 days.

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More particularly, 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 equivalent in progestational activity to 40-150 μg levonorgestrel 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. Following the 23-25-day period, a progestin at a daily dosage equivalent to 10-100 μg levonorgestrel is administered for 3-5 days. The total administration during each cycle is 28 days.

Preferred progestins include, but are not limited to levonorgestrel, norgestrel, desogestrel, 3-ketodesogestrel, norethindrone, gestodene, norethisterone acetate, norgestimate, osaterone, cyproterone acetate, trimegestone, dienogest, and drospirenone. It is more preferred that the progestin is levonorgestrel. When levonorgestrel is used as the progestin during the first 23-25 days of the cycle, it is preferred that the daily dosage of levonorgestrel is 30-150 μg , with 50-100 μg being more preferred, and 90 μg being most preferred. When levonorgestrel is used as the progestin during the last 3-5 days of the cycle, it is preferred that the daily dosage be 10-100 μg , with 20-50 μg levonorgestrel being more preferred, and 37.5 μg most preferred. Preferred dosages of the preferred progestins are provided in the table below.

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PREFERRED DAILY DOSAGE RANGES

	<u>Progestin</u>	<u>First 23-25 Cycle Days</u>	<u>Last 3-5 Cycle Days</u>
	Levonorgestrel	30-150 μg	10-100 μg
	Norgestrel	60-300 μg	20-200 μg
	Desogestrel	45-225 μg	15-150 μg
25	3-Ketodesogestrel	45-225 μg	15-150 μg
	Norethindrone	200 μg - 1 mg	65-650 μg
	Norethisterone Acetate	200 μg - 1 mg	65-650 μg
	Gestodene	20-115 μg	7.5-75 μg
	Norgestimate	75-375 μg	25-250 μg
30	Osaterone	250 μg - 2.5 mg	100 μg - 1.5 mg
	Trimegestone	75-375 μg	25-250 μg
	Dienogest	500 μg - 3.75 mg	100 μg - 2.5 mg
	Drospirenone	500 μg - 3.75 mg	100 μg - 2.5 mg
	Cyproterone Acetate	450 μg - 2.5 mg	150 μg - 1.5 mg

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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 the preferred daily dosage is 10-20 μ g, with 15 μ g being more preferred. When 17 β -estradiol is used as the estrogen, 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 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 progestin be administered for 4 days.

The following daily dosages of a combination of levonorgestrel 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 levonorgestrel for 3-5 days. The total administration during each cycle is 28 days.

PREFERRED DAILY DOSAGES				
	<u>Regimen</u>	<u>First 23-25 Cycle Days</u>		<u>Last 3-5 Cycle Days</u>
		<u>Levonorgestrel</u>	<u>Ethinyl Estradiol</u>	<u>Levonorgestrel</u>
20	A	100 μ g	15 μ g	20-50 μ g
	B	90 μ g	15 μ g	20-50 μ g
	C	75 μ g	15 μ g	20-50 μ g
	D	60 μ g	15 μ g	20-50 μ g
25	E	50 μ g	15 μ g	20-50 μ g
	F	40 μ g	15 μ g	20-50 μ g
	G	100 μ g	10 μ g	10-40 μ g
	H	90 μ g	10 μ g	10-40 μ g
30	I	75 μ g	10 μ g	10-40 μ g
	J	60 μ g	10 μ g	10-40 μ g
	K	50 μ g	10 μ g	10-40 μ g
	L	40 μ g	10 μ g	10-40 μ g

The following daily dosages of a combination of levonorgestrel and ethinyl estradiol are more preferred for contraception when administered for 24 consecutive days beginning on the first day of menses, followed by the administration of

levonorgestrel for 4 days. The total administration during each cycle is 28 days. Of the regimens listed below, Regimens M-O are more preferred, with Regimen N being most preferred.

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MORE PREFERRED DAILY DOSAGES

	Regimen	First 24 Cycle Days		Last 4 Cycle Days
		Levonorgestrel	Ethinyl Estradiol	Levonorgestrel
	M	75 µg	15 µg	37.5 µg
	N	90 µg	15 µg	37.5 µg
10	O	100 µg	15 µg	37.5 µg
	P	50 µg	10 µg	25 µg
	Q	60 µg	15 µg	37.5 µg
	R	75 µg	10 µg	25 µg
	S	40 µg	15 µg	37.5 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.

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EXAMPLE 1

Levonorgestrel, 75 µg
 Ethinyl estradiol, 15 µg
 Microcrystalline Cellulose
 Lactose, NF, Spray Dried
 Polacrillin Potassium, NF
 Magnesium Stearate
 Opadry Pink
 Polyethylene Glycol, 1500, Flakes
 Water, Purified, USP
 Wax E (Pharma)

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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 equivalent to 30-150 μ g levonorgestrel and an estrogen at a daily dosage equivalent to 10-20 μ g ethinyl estradiol for 23-25 days per menstrual cycle 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 a progestin at a daily dosage equivalent to 10-100 μ g levonorgestrel for 3-5 days; wherein the same dosage of the progestin 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 progestin is equal to 28 per menstrual cycle.
2. The method according to claim 1, wherein the combination of progestin and estrogen is administered for 24 days per menstrual cycle beginning on day 1 of the menstrual cycle, followed by the administration of progestin for 4 days per menstrual cycle.
3. The method according to claim 1 or 2, wherein the progestin is selected from the group consisting of levonorgestrel, norgestrel, desogestrel, 3-keto-desogestrel, norethindrone, gestodene, norethisterone acetate, norgestimate, osaterone, cyproterone acetate, trimegestone, dienogest, and drospirenone.
4. The method according to claim 1, 2 or 3, 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.
5. The method according to any one of claims 1 to 4, wherein the progestin is levonorgestrel.
6. The method according to any one of claims 1 to 5, wherein the estrogen is ethinyl estradiol.
7. The method according to any one of claims 1 to 6, wherein levonorgestrel and ethinyl estradiol are administered for 24 days per menstrual cycle beginning on day 1 of the menstrual cycle, followed by the administration of levonorgestrel for 4 days per menstrual cycle.

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8. The method according to claim 7, wherein the daily dosage of levonorgestrel administered during the first 24 days of the menstrual cycle is 50-100 μ g and 20-50 μ g during the last 4 days of the menstrual cycle.
- 5 9. The method according to claims 7 or 8, wherein the daily dosage of levonorgestrel in the combination that is administered for 24 days is 90 μ g; the daily dosage of ethinyl estradiol in the combination that is administered for 24 days is 15 μ g; and the daily dosage of levonorgestrel that is administered for 4 days following the 24-day combination is 37.5 μ g.
- 10 10. The method according to claims 7 or 8, wherein the daily dosage of levonorgestrel in the combination that is administered for 24 days is 75 μ g; the daily dosage of ethinyl estradiol in the combination that is administered for 24 days is 15 μ g; and the daily dosage of levonorgestrel that is administered for 4 days following the 24-day combination is 37.5 μ g.
- 15 11. The method according to claims 7 or 8, wherein the daily dosage of levonorgestrel in the combination that is administered for 24 days is 100 μ g; the daily dosage of ethinyl estradiol in the combination that is administered for 24 days is 15 μ g; and the daily dosage of levonorgestrel that is administered for 4 days following the 24-day combination is 37.5 μ g.
- 20 12. The method according to claims 7 or 8, wherein the daily dosage of levonorgestrel in the combination that is administered for 24 days is 50 μ g; the daily dosage of ethinyl estradiol in the combination that is administered for 24 days is 10 μ g; and the daily dosage of levonorgestrel that is administered for 4 days following the 24-day combination is 25 μ g.
- 25 13. The method according to claims 7 or 8, wherein the daily dosage of levonorgestrel in the combination that is administered for 24 days is 60 μ g; the daily dosage of ethinyl estradiol in the combination that is administered for 24 days is 15 μ g; and the daily dosage of levonorgestrel that is administered for 4 days following the 24-day combination is 37.5 μ g.
- 30 14. The method according to claims 7 or 8, wherein the daily dosage of levonorgestrel in the combination that is administered for 24 days is 75 μ g; the daily dosage of ethinyl estradiol in the combination that is administered for 24 days is 10 μ g; and the daily dosage of levonorgestrel that is administered for 4 days following the 24-day combination is 25 μ g.
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- 12 -

15. The method according to claims 7 or 8, wherein the daily dosage of levonorgestrel in the combination that is administered for 24 days is 40 µg; the daily dosage of ethinyl estradiol in the combination that is administered for 24 days is 15 µg; and the daily dosage of levonorgestrel that is administered for 4 days following the 24-day combination is 37.5 µg.
16. A contraceptive kit adapted for daily oral administration which comprises 28 separate dosage units, 23-25 of said dosage units each containing a combination of progestin at a daily dosage equivalent to 30-150 µg levonorgestrel and an estrogen at a daily dosage equivalent in estrogenic activity to 10-20 µg ethinyl estradiol, wherein each of the 23-25 dosage units contains the same dosage of progestin and estrogen; and 3-5 of said dosage units containing a progestin at a daily dosage equivalent to 10-100 µg levonorgestrel, wherein each of the 3-5 dosage units contains the same dosage of progestin.
17. The contraceptive kit according to claim 16, wherein 24 of the 28 dosage units contain the progestin and estrogen combination, and 4 of the dosage units are estrogen free.
18. The contraceptive kit according to claim 16 or 17, wherein the progestin is selected from the group consisting of levonorgestrel, norgestrel, desogestrel, 3-ketodesogestrel, norethindrone, gestodene, norethisterone acetate, norgestimate, osaterone, cyproterone acetate, trimegestone, dienogest, and drospirenone, and the estrogen is selected from the group consisting of ethinyl estradiol; 17β-estradiol; conjugated estrogens, USP; estrone or a salt thereof; and mestranol.
19. The contraceptive kit according to claim 16, 17 or 18 wherein the estrogen is ethinyl estradiol and the progestin is levonorgestrel.
20. The contraceptive kit according to claim 19 wherein the dosage of levonorgestrel in each of the estrogen containing dosage units is 50-100 µg, and in the estrogen free dosage units is 20-50 µg.
21. The contraceptive kit according to claim 20 wherein the dosage of ethinyl estradiol in each progestin containing dosage unit is 15 µg and the dosage of levonorgestrel in each estrogen containing dosage unit is 90 µg and in each estrogen free dosage unit is 37.5 µg.



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(12) **United States Patent**
Gast(10) **Patent No.:** **US 6,451,778 B1**
(45) **Date of Patent:** **Sep. 17, 2002**(54) **ORAL CONTRACEPTIVE**(75) **Inventor:** **Michael J. Gast, Phoenixville, PA (US)**(73) **Assignee:** **Wyeth, Madison, NJ (US)**(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 677 days.(21) **Appl. No.:** **08/886,072**(22) **Filed:** **Jul. 2, 1997****Related U.S. Application Data**(60) **Provisional application No. 60/022,625, filed on Jul. 26, 1996.**(51) **Int. Cl.⁷** **A61K 31/56**(52) **U.S. Cl.** **514/170; 514/843**(58) **Field of Search** **514/170, 843**(56) **References Cited****U.S. PATENT DOCUMENTS**

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(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.

24 Claims, No Drawings

in each of the three 7-day phases in combination with 50 μ g, 75 μ g, and 100 μ g in the first, second, and third phases, respectively. A third specific triphasic regimen discloses the administration of 35 μ g EE in each of the three 7-day phases in combination with 25 μ g, 35 μ g, and 50 μ g in the first, second, and third phases, respectively.

Lachnit-Fixson (U.S. Pat. No. 4,621,079) discloses triphasic 21-day progestin/estrogen combination regimens in which a combination of 40–70 μ g GTD and 20–35 μ g EE is administered for 4–6 days in the first phase; 50–100 μ g GTD and 30–50 μ g EE is administered for 4–6 days in the second phase; and 80–120 μ g GTD and 20–50 μ g 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. Pat. No. 4,530,839) discloses triphasic 21-day progestin/estrogen combination regimens in which a dose of 20–50 μ g 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 μ g EE in combination with 500 μ g LNg, 750 μ g LNg, and 1 mg LNg during each of the three 7-day phases, respectively.

Edgren (U.S. Pat. No. 4,390,531) discloses triphasic 21-day progestin/estrogen combination regimens in which a dose of 20–40 μ g 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 μ g EE, a second 7 day phase of 1.0 mg NE in combination with 35 μ g EE, and a third 7 day phase of 0.5 mg NE in combination with 35 μ g EE.

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

Erlich (German Patent DE 4,104,385 C1 and U.S. Pat. No. 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 μ g EE followed by 18 days of the combination of 150 μ g LNg and 20 μ g EE. Regimen (c) in Erlich provides a total steroidal load of 2.7 mg of LNg and 560 μ g 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 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.

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

-continued

PREFERRED DAILY DOSAGES		
Regimen	Trimegestone	Ethinyl Estradiol
D	50 μ g	15 μ g
E	40 μ g	15 μ g

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.

PREFERRED DAILY DOSAGES		
Regimen	Dienogest	Ethinyl Estradiol
A	2 mg	15 μ g
B	1 mg	15 μ g
C	800 μ g	15 μ g
D	750 μ g	15 μ g
E	500 μ g	15 μ g

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 μ g
B	2 mg	15 μ g
C	1 mg	15 μ g
D	500 μ g	15 μ g

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)

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 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.

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 μ g trimegestone, and 250 μ g–4 mg dienogest, 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.

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 μ g.

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 μ g.

8. The method according to claim 6, wherein the daily dosage of trimegestone is 125 μ g.

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 trimegestone is 50 μ g.

11. The method according to claim 6, wherein the daily dosage of trimegestone is 40 μ g.

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.

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.

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.

18. 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.

19. The method according to claim 18 in which the non-contraceptive placebo contains an iron supplement.

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(54) Title: MEANS AND METHOD FOR HORMONAL CONTRACEPTION

(57) Abstract: The present invention is concerned with a kit containing a plurality of hormone units for use in a contraceptive method which consists of two alternating consecutive phases, sometimes referred to as a sequential method or sequential regimen. More particularly the present invention relates to a kit containing a plurality of daily hormone units for use in a contraceptive method which consists of two alternating consecutive phases - an estrogenic and a progestogenic phase - of administering a sequence of said hormone units to a female of childbearing capability, the plurality of daily hormone units consisting of: (a) one or more daily hormone units, for use during the estrogenic phase, containing synthetic estrogen or a combination of synthetic estrogen and biogenic estrogen in a therapeutically effective amount to inhibit ovulation and (b) at least 10 daily hormone units, for use during the progestogenic phase, containing a combination of biogenic estrogen and progestogen in a therapeutically effective amount to inhibit ovulation and to transform the endometrium from a proliferative into a secretory state.

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estrogen during the estrogenic phase is insufficient to adequately inhibit follicular development, thereby increasing the risk of ovulation.

DETAILED DESCRIPTION OF THE INVENTION

5 One embodiment of the present invention is concerned with a kit containing a plurality of daily hormone units for use in a contraceptive method, the plurality of daily hormone units consisting of:

- a) one or more daily hormone units containing synthetic estrogen or a combination of synthetic estrogen and biogenic estrogen in an amount equivalent to 3-40 µg ethinyl estradiol and
- 10 b) at least 10 daily hormone units containing biogenic estrogen in an amount equivalent to 0.5-5 mg 17beta-estradiol and progestogen in an amount equivalent to 30-750 µg levonorgestrel.

The one or more daily units containing synthetic estrogen are for use during the estrogenic phase of the method described below, whereas the at least 10 units containing the combination of biogenic estrogen and progestogen are for use during the progestogenic phase. The preferred embodiments described below in relation to the contraceptive method of the invention are equally valid for the above kit, unless they relate to parameters which are only meaningful in relation to a method, i.e. procedure of contraception.

20 Another embodiment of the invention relates to a kit containing hormone units for use in a contraceptive method that consists of two alternating consecutive phases - an estrogenic and a progestogenic phase - said method comprising administering to a female of childbearing capability

- a) during the estrogenic phase one or more hormone units to provide a therapeutically effective amount of synthetic estrogen or a combination of synthetic estrogen and biogenic estrogen to inhibit ovulation and
 - 25 b) during the progestogenic phase one or more hormone units to provide a combination of biogenic estrogen and progestogen in a therapeutically effective amount to inhibit ovulation and to transform the endometrium from a proliferative into a secretory state,
- 30 wherein the progestogenic phase encompasses a period of at least 10 days and the two consecutive phases together encompass a period of 20-35 days.

The term female, whenever referred to in here, relates to female mammals. Preferably the female mammal is a homo sapiens. For homo sapiens females are usually biologically capable of child bearing between the age of 12 and 55.

originally described by McPhail can be used (Mc Phail M.K. "The assay of progestin" J Physiol (1934), 83, 145-156). A more recent description of this method can be found in an article written by Overbeek G.A., de Visser J. "A new substance with progestational activity", Acta Endocrinol (1956), 22, 318-329. It is noted that the aforementioned methods will provide useful indications about the anticipated estrogen potency or progestogen potency of a particular hormone. However, to accurately determine the equivalent amounts that are referred to above, it is advisable to additionally conduct *in vivo* studies in human females.

For guidance the table below provides the conversion factors for a number of progestogens that may suitably be used in the method of the invention. These conversion factors may be used to calculate, for each progestogen mentioned in the table, an estimate of the amount of said progestogen which is equivalent to a given amount of levonorgestrel.

	Conversion factor	equivalent to 30 µg levonorgestrel	equivalent to 750 µg levonorgestrel
levonorgestrel	1	30 µg	750 µg
norethisterone	7	210 µg	5.25 mg
norgestimate	1.7	51 µg	1.275 mg
drospirenone	20	600 µg	15 mg
dydrogesterone	133	4 mg	100 mg

The synthetic estrogen present in the kit according to the invention is preferably selected from the group consisting of: ethinyl estradiol, mestranol, quinestranol, precursors capable of liberating such an estrogen when used in the present contraceptive method and mixtures thereof. Most preferably the synthetic estrogen is ethinyl estradiol or a precursor capable of liberating ethinyl estradiol. The biogenic estrogen is preferably selected from the group consisting of: estradiol, estrone, estran, estriol, estetrol, conjugated equine estrogens, precursors capable of liberating such an estrogen when used in the present method and mixtures thereof. Most preferably the biogenic estrogen is estradiol or a precursor capable of liberating estradiol. Here the term estradiol encompasses both 17alpha-estradiol and 17beta-estradiol. Most preferably the biogenic estrogen is 17beta-estradiol or a precursor thereof.

The progestogen contained in the kit of the invention is preferably selected from the group consisting of levonorgestrel, norgestimate, norethisterone, dydrogesterone, drospirenone, 3-beta-hydroxydesogestrel, 3-keto desogestrel (=etonogestrel), 17-deacetyl

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norgestimate, 19-norprogesterone, acetoxypregnenolone, allylestrenol, anagestone, chlormadinone, cyproterone, demegestone, desogestrel, dienogest, dihydrogesterone, dimethisterone, ethisterone, ethynodiol diacetate, flurogesterone acetate, gastrinon, gestodone, gestrinone, hydroxymethylprogesterone, hydroxyprogesterone, lynestrenol (=lynocestrenol), medrogestone, medroxyprogesterone, megestrol, melengestrol, nomegestrol, norethindrone (=norethisterone), norethynodrel, norgestrel (includes d-norgestrel and dl norgestrel), norgestrienone, normethisterone, progesterone, quingestanol, (17alpha)-17-hydroxy-11-methylene-19-norpregna-4,15-diene-20-yn-3-one, tibolone, algestone acetophenide, nestorone, promegestone, 17-hydroxyprogesterone esters, 19-nor-17hydroxyprogesterone, 17alpha-ethinyl-testosterone, 17alpha-ethinyl-19-nor-testosterone, d-17beta-acetoxy-13beta-ethyl-17alpha-ethinyl-gon-4-en-3-one oxime and precursors of these compounds. Preferably the progestogen used in the progestogenic phase is selected from the group consisting of levonorgestrel, norgestimate, norethisterone, drospirenone, dydrogesterone and their precursors

15 Specific examples of progestogen precursor which may be employed in accordance with the present invention include: anagestone acetate, chlormadinone acetate, cyproterone acetate, gestodene acetate, hydroxymethylprogesterone acetate, hydroxyprogesterone acetate, hydroxyprogesterone hexanoate, hydroxyprogesterone caproate, hydroxyprogesterone enanthate, medroxyprogesterone acetate, megestrol acetate, melengestrol acetate, nomegestrol acetate, norethindrone acetate, norethisterone acetate, norethisterone enanthate, quingestanol acetate, (17alpha)-17-hydroxy-11-methylene-19-norpregna-4,15-diene-20-yn-3-one, tibolone, algestone acetophenide, nestorone, promegestone, 17-hydroxyprogesterone esters, 19-nor-17hydroxyprogesterone esters, 17alpha-ethinyl-testosterone.

25 Best results are obtained with the kit according to the invention when the synthetic estrogen is ethinyl estradiol or a precursor thereof, the biogenic estrogen is estradiol or a precursor thereof and the progestogen is selected from the group consisting of levonorgestrel, norgestimate, norethisterone, drospirenone, dydrogesterone and their precursors. Thus in a preferred embodiment the hormone units for use during the estrogenic phase contain ethinyl estradiol or a combination of ethinyl estradiol and estradiol and/or precursors thereof in a therapeutically effective amount to inhibit ovulation and the hormone units for use during the progestogenic phase contain a therapeutically effective amount of a combination of estradiol and/or a precursor thereof and a progestogen selected from the group consisting of levonorgestrel, norgestimate, norethisterone, drospirenone, dydrogesterone and their precursors, to inhibit ovulation and to transform the endometrium from a proliferative into a

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secretory state. Of the latter progestogens levonorgestrel and norgestimate are particularly preferred.

Throughout this document by precursors of an active ingredient are meant components capable of liberating the active ingredient when used in the present contraceptive method, particularly after administration e.g. as a result of metabolic conversion of the precursor substance. Particularly useful precursors of the hormones present in the kit according to the invention are substances that differ from these hormones in that the hydrogen in at least one of the hydroxyl groups in the hormone-molecule has been substituted by -CO-R, wherein R is a hydrocarbon radical comprising from 1-25 carbons.

It is to be understood that the present invention not only encompasses the use of estrogens and progestogens specifically mentioned in this application, but also metabolites of these hormones that display comparable functionality. In this context it is noted that, for instance, levonorgestrel is a metabolite of norgestimate and that estriol is a metabolite of 17beta-estradiol. Both these progestogens and estrogens have found application in contraceptive formulations and/or preparations for hormone replacement therapy. The plurality of hormone units contained by the present kit can suitably consist of 1-18 daily units for use in the estrogenic phase and 10-27 daily units for use in the progestogenic phase. More preferably the present kit consists of 10-16 daily units for use in the estrogenic phase and 12-18 daily units for use in the progestogenic phase. Most preferably the kit consists of 13-15 daily units for use in the estrogenic phase and 13-15 units for use in the progestogenic phase. The hormone units are preferably for oral administration and arranged in a fixed sequence corresponding to the intended order of administration in 2 phases. Preferably, the hormone units to be used in either the estrogenic or progestogenic phase are easily distinguishable, e.g. because they are different in colour and/or shape. Data indications may be provided on the packaging. The packaging may be a tube or box or a strip. The box may be circular, square, or otherwise shaped with the tablets being accommodated separately therein for ease of administration. Date indications may appear adjacent to each tablet corresponding with the days on which each tablet is to be taken. Some indication of the sequence in which the tablets are to be taken preferably appears on the packaging regardless of its form.

Generally speaking, the hormone units in the present kit are prepared according to conventionally known procedures in accordance with the method of administration. Thus, the active ingredients are prepared according to known methods in a pharmaceutically acceptable form for administration. These ingredients, in their required quantities are combined with the appropriate pharmaceutical carriers such as additives, vehicles and/or flavour ameliorating

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substances. These substances may be referred to as diluents, binders and lubricants. Gums, starches and sugars are also common terms. Typical of these types of substances or excipients are pharmaceutical grades of mannitol, lactose starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate and the like. The active

5 ingredient(s) may comprise from about 0.01% by weight to about 99.99% by weight of the total formulation and the remainder comprises the pharmaceutically acceptable carrier. The percentage of active ingredient(s) may vary according to the delivery system or method of administration and is chosen in accordance with conventional methods known in the art. Thus, the active ingredients are compounded with the chosen carrier and in for example the

10 case of a tablet form, placed in a tablet moulding apparatus to form the tablets which are subsequently packaged in accordance with the chosen regimen.

Another aspect of the present invention relates to the use of synthetic estrogen, biogenic estrogen and progestogen in the manufacture of a kit containing hormone units for use in a contraceptive method that consists of two alternating consecutive phases - an

15 estrogenic and a progestogenic phase - said method comprising administering to a female of childbearing capability

- a) during the estrogenic phase one or more hormone units to provide a therapeutically effective amount of synthetic estrogen or a combination of synthetic estrogen and biogenic estrogen to inhibit ovulation and
- 20 b) during the progestogenic phase one or more hormone units to provide a combination of biogenic estrogen and progestogen in a therapeutically effective amount to inhibit ovulation and to transform the endometrium from a proliferative into a secretory state, wherein the progestogenic phase encompasses a period of at least 10 days and the two consecutive phases together encompass a period of 20-35 days.

25 In the following examples, specific embodiments of the present invention are set forth. These are meant to be illustrative of the invention and are not meant to limit it in any way.

EXAMPLES

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Example 1

Women participating in the study described in these examples are all selected on the basis that they are users of 'high' dose monophasic ethinyl estradiol-containing combined oral contraceptives. The reason for applying this selection criterion is that there is a dose-

CLAIMS

1. A kit containing a plurality of daily hormone units for use in a contraceptive method ,
the plurality of daily hormone units consisting of:
- 5 a) one or more daily hormone units, for use during an estrogenic phase, containing a
synthetic estrogen or a combination of synthetic estrogen and biogenic estrogen in an
amount equivalent to 3-40 µg ethinyl estradiol and
- b) at least 10 daily hormone units, for use during a progestogenic phase, containing biogenic
estrogen in an amount equivalent to 0.5-5 mg 17beta-estradiol and progestogen in an
10 amount equivalent to 30 - 750 µg levonorgestrel.
2. A kit containing a plurality of hormone units for use in a contraceptive method that
consists of two alternating consecutive phases - an estrogenic and a progestogenic phase - said
method comprising administering to a female of childbearing capability
- 15 a) during the estrogenic phase one or more hormone units to provide a therapeutically
effective amount of synthetic estrogen or a combination of synthetic estrogen and
biogenic estrogen to inhibit ovulation and
- b) during the progestogenic phase one or more hormone units to provide a combination of
biogenic estrogen and progestogen in a therapeutically effective amount to inhibit
20 ovulation and to transform the endometrium from a proliferative into a secretory state,
wherein the progestogenic phase encompasses a period of at least 10 days and the two
consecutive phases together encompass a period of 20-35 days.
3. A kit according to claim 1 or 2, wherein the plurality of hormone units consists of 20
25 to 35 daily hormone units, preferably 28 daily hormone units
4. A kit according to any one of claims 1-3, wherein the units for use during the
estrogenic phase also contain a biogenic estrogen.
- 30 5. A kit according to any one of claims 1-4, wherein the units for use during the
progestogenic phase do not contain a synthetic estrogen.

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6. A kit according to any one of claims 2-5, wherein the daily hormone units for use during the estrogenic phase contain the synthetic estrogen in an amount equivalent to 3-40 μg , preferably 15-40 μg ethinyl estradiol.
- 5 7. A kit according to any one of claims 2-6, wherein the daily hormone units for use during the progestogenic phase contain the biogenic estrogen in an amount equivalent to 0.5-5 mg, preferably 1-3 mg 17 β -estradiol.
8. A kit according to any one of claims 2-7, wherein the daily hormone units for use
10 during the progestogenic phase contain the progestogen in an amount equivalent to 30-750 μg , preferably 75-150 μg levonorgestrel.
9. A kit according to any one of claims 1-8, wherein the synthetic estrogen is selected from the group consisting of: ethinyl estradiol, mestranol, quinestranol, precursors capable of
15 liberating such an estrogen when used in the present method and mixtures thereof.
10. A kit according to any one of claims 1-9, wherein the biogenic estrogen is selected from the group consisting of: estradiol, estrone, estran, estriol, estetrol, conjugated equine estrogens, precursors capable of liberating such an estrogen when used in the present method
20 and mixtures thereof.
11. A kit according to any one of claims 1-10, wherein the progestogen is selected from the group consisting of levonorgestrel, norgestimate, norethisterone, dydrogesterone, drospirenone, 3- β -hydroxydesogestrel, etonogestrel, 17-deacetyl norgestimate, 19-
25 norprogesterone, acetoxypregnenolone, allylestrenol, anagestone, chlormadinone, cyproterone, demegestone, desogestrel, dienogest, dihydrogesterone, dimethisterone, ethisterone, ethynodiol diacetate, flurogestone acetate, gastrinon, gestodene, gestrinone, hydroxymethylprogesterone, hydroxyprogesterone, lynestrenol, medrogestone, medroxyprogesterone, megestrol, melengestrol, nomegestrol, norethindrone, norethynodrel,
30 norgestrel, norgestrienone, normethisterone, progesterone, quingestanol, (17 α)-17-hydroxy-11-methylene-19-norpregna-4,15-diene-20-yn-3-one, tibolone, algestone acetophenide, nestorone, promegestone, 17-hydroxyprogesterone esters, 19-nor-17hydroxyprogesterone, 17 α -ethinyl-testosterone, 17 α -ethinyl-19-nor-testosterone, d-

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17beta-acetoxy-13beta-ethyl-17alpha-ethinyl-gon-4-en-3-one oxime and precursors of these compounds.

12. A kit according to any one of claims 1-11, wherein the hormone units for use during the estrogenic phase contain ethinyl estradiol or a combination of ethinyl estradiol and estradiol and/or precursors thereof in a therapeutically effective amount to inhibit ovulation and the hormone units for use during the progestogenic phase contain a combination of estradiol and/or a precursor thereof and a progestogen selected from the group consisting of levonorgestrel, norgestimate, norethisterone, drospirenone, dydrogesterone and their precursors, in a therapeutically effective amount to inhibit ovulation and to transform the endometrium from a proliferative into a secretory state.
13. A kit according to any one of claims 1-12, wherein the plurality of daily hormone units consists of 1-18 units for use in the estrogenic phase and 10-27 units for use in the progestogenic phase.
14. Use of synthetic estrogen, biogenic estrogen and progestogen in the manufacture of a kit containing hormone units for use in a contraceptive method that consists of two alternating consecutive phases - an estrogenic and a progestogenic phase - said method comprising administering to a female of childbearing capability
- a) during the estrogenic phase one or more hormone units to provide a therapeutically effective amount of synthetic estrogen or a combination of synthetic estrogen and biogenic estrogen to inhibit ovulation and
 - b) during the progestogenic phase one or more hormone units to provide a combination of biogenic estrogen and progestogen in a therapeutically effective amount to inhibit ovulation and to transform the endometrium from a proliferative into a secretory state, wherein the progestogenic phase encompasses a period of at least 10 days and the two consecutive phases together encompass a period of 20-35 days.
15. Use according to claim 14, wherein the units for use during the estrogenic phase also contain a biogenic estrogen.
16. Use according to claim 14 or 15, wherein the units for use during the progestogenic phase do not contain a synthetic estrogen.

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17. Use according to any one of claims 14-16, wherein the daily hormone units for use during the estrogenic phase contain the synthetic estrogen in an amount equivalent to 3-40 µg, preferably 15-40 µg ethinyl estradiol.

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18. Use according to any one of claims 14-17, wherein the daily hormone units for use during the progestogenic phase contain the biogenic estrogen in an amount equivalent to 0.5-5 mg, preferably 1-3 mg 17beta-estradiol.

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19. Use according to any one of claims 14-18, wherein the daily hormone units for use during the progestogenic phase contain the progestogen in an amount equivalent to 30-750 µg, preferably 75-150 µg levonorgestrel.

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20. Use according to any one of claims 14-19, wherein the hormone units for use during the estrogenic phase contain ethinyl estradiol or a combination of ethinyl estradiol and estradiol and/or precursors thereof in a therapeutically effective amount to inhibit ovulation and the hormone units for use during the progestogenic phase contain a therapeutically effective amount of a combination of estradiol and/or a precursor thereof and a progestogen selected from the group consisting of levonorgestrel, norgestimate, norethisterone, drospirenone, dydrogesterone and their precursors, to inhibit ovulation and to transform the endometrium from a proliferative into a secretory state.

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21. Use according to any one of claims 14-20, wherein the plurality of daily hormone units consists of 1-18 units for use in the estrogenic phase and 10-27 units for use in the progestogenic phase.



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(12) **United States Patent**
Boissonneault et al.

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(54) **CHEWABLE ORAL CONTRACEPTIVE**

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(52) U.S. Cl. **424/439; 424/400; 424/440;**
424/441; 424/464; 424/484; 424/489; 514/841;
514/843

(58) Field of Search **424/400, 439,**
424/440, 441, 464, 484, 489; 514/841,
843

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Hauer & Feld, L.L.P.

(57) **ABSTRACT**

The present invention relates to a chewable, palatable oral contraceptive tablet, comprising an oral contraceptive agent, a chewable carrier suitable for human consumption, and not comprising a ferrocene compound, as well as use of these tablets in a method of human female oral contraception, and in a method of enhancing compliance with a human female oral contraceptive regimen.

60 Claims, No Drawings

CHEWABLE ORAL CONTRACEPTIVE

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a continuation-in-part of U.S. patent application Ser. No. 09/286,908, filed Apr. 6, 1999.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

Not Applicable.

REFERENCE TO MICROFICHE APPENDIX

Not Applicable.

BACKGROUND OF THE INVENTION

The present invention generally relates to an oral contraceptive delivery system, and in particular an oral contraceptive delivery system involving novel alternate dose forms to improve compliance.

The efficacy of oral contraceptives tends to be particularly patient compliance dependent, largely due to the lack of a disease state or symptoms to remind a human female patient (sometimes referred to simply as "patient" or "woman") to take a pill. The single most significant reason for failure with oral contraceptives is use, rather than method, failure. That is, unless the contraceptives are used according to the prescribed regimen, the contraceptives can fail to effectively help a patient avoid pregnancy. Further, in order to be most effective in preventing pregnancy and maintaining menstrual cycle control, proper compliance with an oral contraceptive dosage regimen requires that the oral contraceptives be taken at about the same time each day.

Various attempts have been made to improve patient compliance with contraceptive regimens. For example, it has been suggested that progestin rods can be inserted subdermally. This procedure has been described, for example, in U.S. Pat. No. 5,756,115. This technique has the significant disadvantage of requiring a surgical incision, a procedure that is highly disfavored by a relatively large segment of the patient population.

As another example, it has been suggested that DEPO-PROVERA® (Pharmacia, Inc.) medroxyprogesterone acetate can be injected subcutaneously every three months. This technique has been described, for example, in U.S. Pat. No. 4,639,439. This procedure has the disadvantage of requiring an injection via hypodermic needle, which is also a procedure that is disfavored by many patients.

In many cases, the patient prefers to carry the contraceptive pills on her person as a matter of lifestyle or personal discretion. This is especially true for younger patients, and it is not uncommon for such patients to exchange pills. Members of this population tend to view portable packaging of the pills, immediate access to the pills, and ease of pill use as significant benefits.

Prior proposed solutions to the compliance problem have tended to focus primarily or exclusively on optimizing compliance packaging, rather than on changes to the dosage form. It has been suggested that instead of being packaged in vials, contraceptive pills can be packaged in 21 or 28 day blister packages. It has also been suggested that the size of these packages can be reduced to improve portability and confidentiality.

Although oral contraceptive pills provided in a small blister package are somewhat more convenient to carry and

to conceal, they are not necessarily easy to ingest. Access to water to facilitate contraceptive pill taking remains a problem. Most medications are typically stored in a medicine cabinet and therefore are likely to be near a water source. On the contrary, oral contraceptive pills are often carried on the person and a source of water is not always available when it is time to take the oral contraceptive pill. Additionally, a certain segment of the patient population will have trouble swallowing pills, irrespective of access to water.

The present invention provides an improved oral contraceptive tablet. The technology encompassed in the invention involves a chewable, palatable oral contraceptive tablet that has appropriate size and hardness for blister packaging and compliant use.

BRIEF SUMMARY OF THE INVENTION

One aspect of the present invention relates to a chewable, palatable oral contraceptive tablet, comprising an oral contraceptive agent, a chewable carrier suitable for human consumption, and not comprising a ferrocene compound.

Another aspect of this invention relates to a method of human female oral contraception, the method comprising providing a chewable, palatable oral contraceptive tablet comprising a contraceptively effective amount of an oral contraceptive agent, and a chewable carrier suitable for human consumption, and not comprising a ferrocene compound, and administering the tablet to a human female.

Yet another aspect of this invention relates to a method of enhancing compliance with a human female oral contraceptive regimen involving oral contraceptive tablets, the method comprising providing chewable, palatable oral contraceptive tablets comprising a contraceptively effective amount of an oral contraceptive agent, and a chewable carrier suitable for human consumption, and not comprising a ferrocene compound, and administering the tablets to the human female in accordance with the contraceptive regimen.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

Not Applicable.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to chewable, palatable oral contraceptive tablets for administering an oral contraceptive agent to human females. The tablets of this invention may simply be chewed, and therefore are easy for a patient to ingest, even in the absence of a liquid. The oral contraceptive agent formulation of this invention improves dosage regimen compliance, and thereby enhances the desired contraceptive effect of the oral contraceptive. This invention also includes methods for administering the oral contraceptive formulations to a woman.

Definitions

The articles "a" and "an" are used herein to refer to one or more than one (i.e., to at least one) of the grammatical objects of the article. By way of example, "an element" means one element or more than one element.

The term "oral contraceptive agent," as used herein, refers to any compound or combination of compounds which, when administered orally, prevents pregnancy.

The term "estrogen," as used herein, refers to any natural or synthetic compound which exhibits an effect on the

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female reproductive organs in a manner similar to the natural female hormone estrogen. Examples of an estrogen include, but are not limited to, ethinyl estradiol, estradiol, estradiol valerate, and estradiol acetate.

The term "progestin," as used herein, refers any natural or synthetic compound which exhibits a progestational effect on the female reproductive organs. Examples of a progestin include, but are not limited to, norethindrone, norethindrone acetate, desogestrel, levonorgestrel, ethynodiol diacetate, norgestrel, norgestimate, gestodene, drospirenone, trimegestone, levodesogestrel, gestodyne and nesterone.

The term "palatable," as used herein, means that the tablet of this invention has a taste, mouth feel, chewability, texture, aroma, and lack of grittiness and bad aftertaste that makes the tablet agreeable to a woman to chew.

levonorgestrel, ethynodiol diacetate, norgestrel, norgestimate, gestodene, drospirenone, trimegestone, levodesogestrel, gestodyne, and nesterone. Preferably, the progestin is norethindrone.

The dosage of the oral contraceptive agent employed would tend to be that conventionally used in the art for the particular oral contraceptive agent selected. The proportion of the oral contraceptive agent in the tablet may be a pharmaceutically effective trace amount to about 10% by weight. Thus, the quantity of oral contraceptive agent per tablet may be varied as desired, typically about 10 micrograms to about 5 milligrams, but the lower and upper dosages may be reduced or increased. Examples of approximate dosage ranges of oral contraceptive agents in milligrams per tablet are summarized in Table 1.

TABLE 1

Examples of Dose Ranges of Oral Contraceptive Agents (milligrams per tablet)				
Description	Examples	Broad	Intermediate	Preferred
Progestin	Norethindrone,	0.1 to 2.5	0.25 to 2.0	0.4 to 1.5
	Norethindrone acetate	0.1 to 2.5	0.25 to 2.0	0.4 to 1.5
	Desogestrel	0.05 to 0.5	0.1 to 0.3	0.1 to 0.2
	Levonorgestrel	0.025 to 1.5	0.025 to 1.0	0.05 to 0.6
	Ethinodiol diacetate	0.5 to 2.5	0.75 to 1.25	0.9 to 1.1
	Norgestrel	0.05 to 3.0	0.05 to 2.0	0.1 to 1.2
	Norgestimate	0.1 to 0.5	0.15 to 0.35	0.18 to 0.25
	Gestodene	0.03 to 0.15	0.05 to 0.10	0.06 to 0.075
	Drospirenone	1.0 to 5.0	2.0 to 4.0	2.5 to 3.5
	Trimegestone	0.05 to 0.5	0.1 to 0.3	0.1 to 0.2
	Ethinyl Estradiol,	0.01 to 0.075	0.015 to 0.05	0.020 to 0.050
Estrogen	Estradiol	0.5 to 4.0	1 to 3	1.5 to 2.5
	Estradiol valerate	0.5 to 5.0	1.5 to 3.5	1.9 to 3.0
	Estradiol acetate	0.5 to 5.0	1.5 to 3.5	1.8 to 3.0

A tablet is "chewable," as used herein, such that when the tablet is chewed, it breaks into smaller pieces that can be swallowed. This is in contrast to gum, for example, which does not break into smaller pieces when chewed.

Description of the Invention

The first aspect of the invention relates to a chewable, palatable oral contraceptive tablet comprising an oral contraceptive agent, a chewable carrier suitable for human consumption and not comprising a ferrocene compound. The tablet of this invention expressly does not contain a ferrocene compound. Ferrocene compounds are used in the treatment of anemia and it should not be assumed that all patients desiring an oral contraceptive agent are anemic. Administering ferrocene compounds when they are not needed can lead to iron poisoning. Additionally, ferrocene compounds may not be palatable when chewed.

In principle, virtually any oral contraceptive agent used in human medicine could be employed in accordance with the principles of the present invention. The oral contraceptive agent may be an estrogen, a progestin, or a combination of an estrogen and a progestin. In one embodiment, the oral contraceptive agent is an estrogen selected from the group consisting of ethinyl estradiol, estradiol, estradiol valerate, and estradiol acetate. Preferably, the estrogen is ethinyl estradiol.

In another embodiment, the oral contraceptive agent is a progestin selected from the group consisting of norethindrone, norethindrone acetate, desogestrel,

In one preferred embodiment, the tablet comprises estrogen in the form of ethinyl estradiol in an amount of about 10 micrograms to about 75 micrograms. In another preferred embodiment, the tablet comprises progestin in the form of norethindrone in an amount of about 0.1 milligram to about 2.5 milligrams.

The invention also includes a tablet in which the oral contraceptive agent is a combination of an estrogen and a progestin. Preferably, the estrogen is ethinyl estradiol and the progestin is norethindrone. In a more preferred embodiment, the amount of ethinyl estradiol in the tablet is about 10 micrograms to about 75 micrograms and the amount of norethindrone in the tablet is about 0.1 milligram to about 2.5 milligrams.

The tablets of this invention can be used in conjunction with an oral contraceptive regimen. The regimen can comprise administering tablets on a daily basis for multiple consecutive days. As such, throughout the duration of the regimen the amount of oral contraceptive agent in the oral contraceptive tablets may remain constant, thereby comprising a uniphasic regimen. Additionally, the amount of oral contraceptive agent in the oral contraceptive tablets may vary throughout the duration of the regimen, thereby comprising a multiphasic regimen. In tablets comprising an estrogen and a progestin, the ratio of the estrogen to the progestin can be constant throughout the duration of the regimen. Additionally, the ratio of the estrogen to the progestin in the oral contraceptive tablets can vary throughout the regimen.

It is also possible to form placebo tablets which otherwise correspond in composition to the tablet of the present invention but are free of the oral contraceptive agent.

The oral contraceptive agent may be present in a carrier either in a dissolved or a uniformly suspended state. A carrier comprises all but the active oral contraceptive agent or agents and includes an inactive ingredient or a combination of one or more inactive ingredients. The carrier imparts chewable and palatable characteristics to the tablet and must be suitable for human consumption, that is, free of harmful amounts of any toxins or components that are adverse to humans. All ingredients in the carrier should be generally recognized as safe (GRAS), as determined by the Food and Drug Administration (FDA) or the Flavor and Extract Manufacturers' Association (FEMA). The carrier selected for the invention must be chewable and should not confer a disagreeable taste to the tablet. Thus, the carrier itself must be palatable. The primary ingredient of a carrier is one or more diluents. Non-limiting examples of diluents that can be used in accordance with this invention include microcrystalline cellulose, corn starch, modified starch, calcium carbonate, dicalcium phosphate, and poly-alcohol sugars such as dextrose, mannitol, sorbitol, xylitol, lactose, sucrose, and fructose. Many other diluents or other ingredients suitable as components of carriers for a chewable, palatable oral contraceptive tablet are available and would be well known to those skilled in the art in view of the present disclosure.

In another aspect of the invention, the tablet optionally further comprises at least one of a flavor agent, a sweetener, and a color agent. A flavor agent can be used to enhance the taste of the tablet, making the tablet more palatable than a tablet without a flavor agent. Spray dried flavor agents are preferred because they are easy to incorporate into a chewable tablet. Non-limiting examples of preferred flavor agents impart the following flavors: strawberry, wild berry, spearmint, wintergreen, black cherry, orange, orange cream, and lemon. The flavoring agents are readily available from many commercial sources. Exemplary compounds suitably used in preparing flavors are listed in G. Burdock, Ed., *Fenaroli's Handbook of Flavor Ingredients*, 3rd edition, Volumes I and II, CRC Press, New York, 1995. Other flavors and flavoring agents suitable for the tablet would be well known to those skilled in the art in view of the present disclosure.

A sweetener can also be used to enhance to taste of the tablet, making the tablet more palatable than a tablet without a sweetener. Sweeteners include natural sugars and artificial sugar substitutes. Non-limiting examples of sweeteners that can be used in accordance with this invention include aspartame, sucralose, xylitol, sorbitol, mannitol, dextrose, sucrose, and fructose. Non-limiting examples of the amount of flavor agents or sweeteners that can be used in the tablet composition of the present invention are listed in Table 2. The amounts in Table 2 are given as percentage of the total tablet weight.

TABLE 2

Ingredient Type	Sweetener and Flavor Amounts Used in Chewable Oral Contraceptive Formulations			
	Examples	Broad	Intermediate	Preferred
Sweetener	Aspartame	0.02 to 1.0%	0.02% to 0.2%	0.03% to 0.05%
	Sucralose	0.01 to 0.5%	0.01% to 0.1%	0.02 to 0.04%

TABLE 2-continued

Ingredient Type	Sweetener and Flavor Amounts Used in Chewable Oral Contraceptive Formulations			
	Examples	Broad	Intermediate	Preferred
Flavor Agent	Spearmint	0.5 to 5%	1 to 3%	1.5 to 2.5%
	Wintergreen	0.5 to 5%	1 to 3%	1.5 to 2.5%
	Wild berry	0.1 to 3%	0.2 to 1%	0.3 to 0.5%

Optionally, a color agent may be added to aid in tablet identification and to enhance the visual appearance of the tablet. A visually pleasing color enhances patient acceptance and thereby compliance with an oral contraceptive regimen. The color agent may be any that are well known to those in the tablet-making art in view of the present disclosure, and could be used in any amount to impart the desired color.

The tablet can be manufactured by standard pharmaceutical techniques of solid dose formulation, such as granulation and compression. These processes are well known to those skilled in the art of making tablets (See Lieberman, Lachman, and Schwartz, *Pharmaceutical Dosage Forms*, Volume 1, New York, 1989). During the granulation process, other ingredients typically used in tablet formulation for human consumption can be included, such as binders, lubricants, anti-adherents, glidants, disintegrants and fillers or other optional ingredients that do not adversely affect chewability or palatability of the tablet or its active oral contraceptive agent ingredient(s).

Binders aid the formation of granulated particles of active oral contraceptive agents and carrier ingredients. Non-limiting examples of binders include glucose, acacia, guar gum, gelatin, simple syrup, sucrose, sorbitol, starch, alginate acid, alginate salts, polyethylene glycol, polyvinylpyrrolidone, polymethacrylates, pregelatinized starch, and celluloses such as methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, and ethylcellulose. A solution of binder is prepared (concentrations dependent on the particular binder used), and the binder solution is mixed with the other excipients to form the wet granulation. A binder such as polyvinylpyrrolidone (Povidone) is typically used in a solution of about 3% to about 15% by weight and is added to the other tablet ingredients resulting in a final formulation concentration of about 2% to about 5%. Similarly, cellulose derivatives are typically used in granulating solutions of about 5% to about 10% by weight and concentrations would be known to one skilled in the art of making tablets using wet granulation in view of the present disclosure.

Disintegrants facilitate breakup of the tablet after administration during chewing. Non-limiting examples of disintegrants include croscopovidone, croscarmellose sodium, starches, corn starch, potato starch, modified corn starch, sodium starch glycolate, and pregelatinized starch. Disintegrants can be included in the tablet formulation in amounts generally less than about 25% of the tablet weight, preferably less than about 20%, and more preferably about 1 to about 20% (natural starches such as corn or potato starch), about 5 to about 10% (pregelatinized starch), and about 3 to 8% (modified corn starch). Croscopovidone and croscarmellose sodium are used at levels of about 5% or lower.

As a final step in the manufacture of the tablet, a lubricant, an anti-adherent, and a glidant can be added to the tablet

granulation. A lubricant facilitates tablet manufacture by reducing friction in the tablet die during compression and ejection. An anti-adherent prevents the tablet from sticking to the tablet punch and die wall. A glidant improves flow characteristics of the granulation. Non-limiting examples of a lubricant include stearates, such as magnesium, calcium, and sodium stearates, stearic acid, hydrogenated vegetable oils, waxes, talc, boric acid, sodium benzoate, sodium acetate, sodium chloride, DL-leucine, sodium oleate, sodium lauryl sulfate, magnesium lauryl sulfate, and CARBOWAX® (Union Carbide Chemicals & Plastics Technology Corp.) polyethylene glycols. Non-limiting examples of an anti-adherent include talc, corn starch, colloidal silicon dioxide, DL-leucine, sodium lauryl sulfate, and metallic stearates. Non-limiting examples of a glidant include talc, corn starch, and colloidal silicon dioxides such as CAB-O-SIL® (Cabot Corp.), SYLOID® (W.R. Grace & Co.), and AEROSIL® (Degussa). Some ingredients, such as talc, can contribute to the formulation with combined functions, acting as a lubricant, and an anti-adherent, and a glidant.

A lubricant is typically included in the tablet formulation in amounts less than about 10% of the tablet weight, preferably less than about 6%, and more preferably about 0.25 to about 2% (stearates, stearic acid, hydrogenated vegetable oil), about 1 to about 5% (talc, waxes, DL-leucine, CARBOWAX®, sodium lauryl sulfate), about 1 to about 2% (magnesium lauryl sulfate) and about 4 to about 6% (sodium chloride, sodium oleate, sodium benzoate, sodium acetate).

Anti-adherents are typically included in the tablet formulation in amounts generally less than about 15% of the tablet weight, preferably less than about 12%, and more preferably about 3 to about 10% (cornstarch, DL-leucine), about 1 to about 5% (talc), about 0.1 to about 0.5% (colloidal silicon dioxide) and less than about 1% (sodium lauryl sulfate, metallic stearates).

A glidant is typically included in the tablet formulation in amounts generally less than about 15% of the tablet weight, preferably less than about 12%, and more preferably less than about 5 to about 10% (corn starch), about 0.1 to about 0.5% (CAB-O-SIL®, SYLOID®), about 1 to about 3% (AEROSIL®), and about 5% (talc).

The chewable tablet generally is not coated with a film or sugar coating. However, thin tablet coatings of a type known to those skilled in making coated tablets can be used.

In one preferred embodiment of the invention, the oral contraceptive agent comprises norethindrone and ethinyl estradiol, the carrier comprises dicalcium phosphate, lactose monohydrate, and maltodextrin, and the tablet further comprises sucralose, a flavor agent, sodium starch glycolate, povidone, and magnesium stearate.

The overall size of the tablet may be any tablet size that incorporates the desired contraceptively effective amount of the oral contraceptive agent and the carrier and is still chewable and palatable. In a preferred embodiment, the size of the tablet is small, on the order of about 50 milligrams to about 300 milligrams. More preferably, the tablet weight is about 70 milligrams to about 120 milligrams, and most preferably, the tablet weight is about 90 milligrams to about 110 milligrams. A smaller tablet is more portable than a larger tablet and therefore more appealing to patients preferring to carry oral contraceptive pills on their person, particularly in blister packaging. Further, smaller tablets are more likely than larger tablets to be accepted as chewable. Therefore, smaller tablets are more likely to enhance a patient's compliance with an oral contraceptive regimen. The shape of the tablet of the present invention is not critical.

The hardness of the tablet may be any hardness that allows for tablet formation and that is still palatable and chewable. One aspect of the invention includes a tablet having a hardness sufficient for blister packaging while still remaining palatable and chewable. Blister packaging is common in the art of oral contraceptive tablet dispensing. In a preferred embodiment, the tablet of the invention has a hardness of about 5 kilopond (kp) to about 15 kp, and preferably about 7 kp to about 12 kp.

Another aspect of this invention relates to a method of human female oral contraception comprising providing a chewable, palatable oral contraceptive tablet comprising a contraceptively effective amount of an oral contraceptive agent, and a chewable carrier suitable for human consumption, and not comprising a ferrocene compound, and administering the tablet to a human female. The tablet is the tablet described above, and typically and preferably, a number of such tablets as part of a contraceptive regimen.

The tablet can be administered to the woman in a variety of ways. Typically, the tablet is administered once daily. The tablet routinely contains a contraceptively active amount of an oral contraceptive agent, and some tablets used in a regimen may be a placebo. The placebo tablets are administered on days where the oral contraceptive agent is not required. As such, the woman is administered a tablet every day to help maintain the contraceptive regimen of taking a daily tablet. For example, a dosage regimen may utilize about 21 to about 63 days of tablets containing the oral contraceptive agent followed by about 3 to about 7 days of tablets comprising a placebo. Preferably, the regimen entails administering tablets for total of about 24 to about 32 days, wherein tablets containing the oral contraceptive agent are administered for about 21 to about 25 days, followed by about 3 to about 7 days of placebo tablets not containing the contraceptive. In one preferred embodiment, the tablets are administered for a total of about 28 days.

As explained above, the contraceptive dosage in the tablets can be uniphasic or multiphasic.

Another aspect of this invention relates to a method of enhancing compliance with a human female oral contraceptive regimen involving oral contraceptive tablets, the method comprising providing chewable, palatable oral contraceptive tablets comprising a contraceptively effective amount of an oral contraceptive agent, and a chewable carrier suitable for human consumption, and not comprising a ferrocene compound, and administering the tablets to the human female in accordance with the contraceptive regimen.

In connection with this aspect of the invention, each tablet of the regimen preferably comprises a daily dosage of the oral contraceptive agent. As such, daily administration of one of the tablets would be part of the regimen. The chewable, palatable oral contraceptive of this invention allows the woman the convenience of ingesting the tablet in a manner that does not require taking the tablet with liquid, without chewing it. Therefore, the woman can take the tablet each day at a time and place that is suitable to her lifestyle. Ingesting the tablets at the same time of day on a daily basis enhances compliance with any given contraceptive regimen.

The regimen can comprise any number of days of administration of the tablets to the woman. In one preferred embodiment, the regimen comprises providing about 21 to about 63 tablets, each tablet comprising the daily dosage of the oral contraceptive agent, followed by about 3 to about 7 tablets, each comprising a placebo. Preferably, a total of about 24 to about 32 tablets are administered daily, wherein

EXAMPLE 4

Composition of a 100 milligram tablet		
Ingredient Type	Ingredient	Amount (milligrams/tablet)
Oral Contraceptive Agent	Norethindrone	0.40
Oral Contraceptive Agent	Ethinyl Estradiol	0.035
Diluent	Mannitol	97
Flavor Agent	Strawberry	2
Lubricant	Magnesium stearate	0.5

EXAMPLE 6

Composition of a 100 milligram tablet		
Ingredient Type	Ingredient	Amount (milligrams/tablet)
Oral Contraceptive Agent	Norethindrone	0.40
Oral Contraceptive Agent	Ethinyl Estradiol	0.035
Diluent	Dextrose	60
Diluent	Lactose	37
Flavor Agent	Strawberry	2
Lubricant	Magnesium stearate	0.5

EXAMPLE 6

Composition of a 120 milligram tablet		
Ingredient Type	Ingredient	Amount (milligrams/tablet)
Oral Contraceptive Agent	Norethindrone	0.40
Oral Contraceptive Agent	Ethinyl Estradiol	0.035
Diluent	Dicalcium Phosphate	20.8
Diluent	Lactose Monohydrate	20.8
Diluent	Dextrose	70
Diluent	Maltodextrin	0.16
Sweetener	Sucralose	0.02
Flavor Agent	Spearmint	1.8
Disintegrant	Sodium starch glycolate	4.1
Binder	Povidone	1.5
Lubricant	Magnesium stearate	0.41

It will be appreciated by those skilled in the art that changes could be made to the embodiments described above without departing from the broad inventive concept thereof. It is understood, therefore, that this invention is not limited to the particular embodiments disclosed, but it is intended to cover modifications within the spirit and scope of the present invention as defined by the appended claims.

We claim:

1. A chewable, palatable oral contraceptive tablet, comprising an oral contraceptive agent, a chewable carrier suitable for human consumption, wherein the contraceptive tablet is chewable and palatable and does not contain a ferrocene compound.

2. The tablet of claim 1, wherein the oral contraceptive agent is selected from the group consisting of an estrogen, a progestin, and a combination thereof.

3. The tablet of claim 2, wherein the carrier is selected from the group consisting of dicalcium phosphate, lactose, corn starch, microcrystalline cellulose, maltodextrin, dextrose, mannitol, sorbitol, xylitol, fructose, sucrose, and calcium carbonate.

4. The tablet of claim 1, wherein the carrier is selected from the group consisting of dicalcium phosphate, lactose, corn starch, microcrystalline cellulose, maltodextrin, dextrose, mannitol, sorbitol, xylitol, fructose, sucrose, and calcium carbonate.

5. The tablet of claim 1, wherein the oral contraceptive agent comprises an estrogen.

6. The tablet of claim 5, wherein the estrogen is selected from the group consisting of ethinyl estradiol, estradiol, estradiol valerate, and estradiol acetate.

7. The tablet of claim 6, wherein the carrier is selected from the group consisting of dicalcium phosphate, lactose, corn starch, microcrystalline cellulose, maltodextrin, dextrose, mannitol, sorbitol, xylitol, fructose, sucrose, and calcium carbonate.

8. The tablet of claim 1, wherein the oral contraceptive agent comprises a progestin.

9. The tablet of claim 8, wherein the progestin is selected from the group consisting of norethindrone, norethindrone acetate, desogestrel, levonorgestrel, ethynodiol diacetate, norgestrel, norgestimate, gestodene, drospirenone, trimegestone, levodesogestrel, gestodyne, and nesterone.

10. The tablet of claim 9, wherein the carrier is selected from the group consisting of dicalcium phosphate, lactose, corn starch, microcrystalline cellulose, maltodextrin, dextrose, mannitol, sorbitol, xylitol, fructose, sucrose, and calcium carbonate.

11. The tablet of claim 1, wherein the oral contraceptive agent comprises an estrogen and a progestin.

12. The tablet of claim 11, wherein the estrogen is selected from the group consisting of ethinyl estradiol, estradiol, estradiol valerate, and estradiol acetate, and the progestin is selected from the group consisting of norethindrone, norethindrone acetate, desogestrel, levonorgestrel, ethynodiol diacetate, norgestrel, norgestimate, gestodene, drospirenone, trimegestone, levodesogestrel, gestodyne, and nesterone.

13. The tablet of claim 12, wherein the carrier is selected from the group consisting of dicalcium phosphate, lactose, corn starch, microcrystalline cellulose, maltodextrin, dextrose, mannitol, sorbitol, xylitol, fructose, sucrose, and calcium carbonate.

14. The tablet of claim 13, further comprising at least one of a flavor agent, a sweetener, and a color agent.

15. The tablet of claim 1, wherein the tablet weighs about 50 milligrams to about 300 milligrams.

16. The tablet of claim 1, wherein the tablet has a hardness sufficient for blister packaging.

17. The tablet of claim 1, wherein the tablet has a hardness of about 5 kiloponds to about 15 kiloponds.

18. The tablet of claim 1, wherein the oral contraceptive agent comprises norethindrone and ethinyl estradiol, the carrier comprises dicalcium phosphate, lactose monohydrate, and maltodextrin, and the tablet further comprises sucralose, a flavor agent, sodium starch glycolate, povidone, and magnesium stearate.

19. A method of human female oral contraception, the method comprising providing a chewable, palatable oral contraceptive tablet comprising a contraceptively effective amount of an oral contraceptive agent, and a chewable carrier suitable for human consumption, and does not contain a ferrocene compound, and administering the tablet to a human female.

20. The method of claim 19, wherein the oral contraceptive agent is selected from the group consisting of an estrogen, a progestin, and a combination thereof.

21. The method of claim 20, wherein the carrier is selected from the group consisting of dicalcium phosphate, lactose, corn starch, microcrystalline cellulose, maltodextrin, dextrose, mannitol, sorbitol, xylitol, fructose, sucrose, and calcium carbonate.

22. The method of claim 19, wherein the carrier is selected from the group consisting of dicalcium phosphate,

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lactose, corn starch, microcrystalline cellulose, maltodextrin, dextrose, mannitol, sorbitol, xylitol, fructose, sucrose, and calcium carbonate.

23. The method of claim 19, wherein the oral contraceptive agent comprises an estrogen.

24. The method of claim 23, wherein the estrogen is selected from the group consisting of ethinyl estradiol, estradiol, estradiol valerate, and estradiol acetate.

25. The method of claim 24, wherein the carrier is selected from the group consisting of dicalcium phosphate, lactose, corn starch, microcrystalline cellulose, maltodextrin, dextrose, mannitol, sorbitol, xylitol, fructose, sucrose, and calcium carbonate.

26. The method of claim 19, wherein the oral contraceptive agent comprises a progestin.

27. The method of claim 26, wherein the progestin is selected from the group consisting of norethindrone, norethindrone acetate, desogestrel, levonorgestrel, ethynodiol diacetate, norgestrel, norgestimate, gestodene, drospirenone, trimegestone, levodesogestrel, gestodyne, and nesterone.

28. The method of claim 27, wherein the carrier is selected from the group consisting of dicalcium phosphate, lactose, corn starch, microcrystalline cellulose, maltodextrin, dextrose, mannitol, sorbitol, xylitol, fructose, sucrose, and calcium carbonate.

29. The method of claim 19, wherein the oral contraceptive agent comprises an estrogen and a progestin.

30. The method of claim 29, wherein the estrogen is selected from the group consisting of ethinyl estradiol, estradiol, estradiol valerate, and estradiol acetate, and the progestin is selected from the group consisting of norethindrone, norethindrone acetate, desogestrel, levonorgestrel, ethynodiol diacetate, norgestrel, norgestimate, gestodene, drospirenone, trimegestone, levodesogestrel, gestodyne, and nesterone.

31. The method of claim 30, wherein the carrier is selected from the group consisting of dicalcium phosphate, lactose, corn starch, microcrystalline cellulose, maltodextrin, dextrose, mannitol, sorbitol, xylitol, fructose, sucrose, and calcium carbonate.

32. The method of claim 31, wherein the tablet further comprises at least one of a flavor agent, a sweetener, and a color agent.

33. The method of claim 19, wherein the tablet weighs about 50 milligrams to about 300 milligrams.

34. The method of claim 19, wherein the tablet has a hardness sufficient for blister packaging.

35. The method of claim 19, wherein the tablet has a hardness of about 5 kiloponds to about 15 kiloponds.

36. The method of claim 19, wherein the oral contraceptive agent comprises norethindrone and ethinyl estradiol, the carrier comprises dicalcium phosphate, lactose monohydrate, and maltodextrin, and the tablet further comprises sucralose, a flavor agent, sodium starch glycolate, povidone, and magnesium stearate.

37. A method of enhancing compliance with a human female oral contraceptive regimen involving oral contraceptive tablets, the method comprising providing chewable, palatable oral contraceptive tablets comprising a contraceptively effective amount of an oral contraceptive agent, and a chewable carrier suitable for human consumption, and not comprising a ferrocene compound, and administering the tablets to the human female in accordance with the contraceptive regimen.

38. The method of claim 37, wherein the oral contraceptive agent is selected from the group consisting of an estrogen, a progestin, and a combination thereof.

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39. The method of claim 38, wherein the carrier is selected from the group consisting of dicalcium phosphate, lactose, corn starch, microcrystalline cellulose, maltodextrin, dextrose, mannitol, sorbitol, xylitol, fructose, sucrose, and calcium carbonate.

40. The method of claim 37, wherein the carrier is selected from the group consisting of dicalcium phosphate, lactose, corn starch, microcrystalline cellulose, maltodextrin, dextrose, mannitol, sorbitol, xylitol, fructose, sucrose, and calcium carbonate.

41. The method of claim 37, wherein the oral contraceptive agent comprises an estrogen.

42. The method of claim 41, wherein the estrogen is selected from the group consisting of ethinyl estradiol, estradiol, estradiol valerate, and estradiol acetate.

43. The method of claim 42, wherein the carrier is selected from the group consisting of dicalcium phosphate, lactose, corn starch, microcrystalline cellulose, maltodextrin, dextrose, mannitol, sorbitol, xylitol, fructose, sucrose, and calcium carbonate.

44. The method of claim 37, wherein the oral contraceptive agent comprises a progestin.

45. The method of claim 44, wherein the progestin is selected from the group consisting of norethindrone, norethindrone acetate, desogestrel, levonorgestrel, ethynodiol diacetate, norgestrel, norgestimate, gestodene, drospirenone, trimegestone, levodesogestrel, gestodyne, and nesterone.

46. The method of claim 45, wherein the carrier is selected from the group consisting of dicalcium phosphate, lactose, corn starch, microcrystalline cellulose, maltodextrin, dextrose, mannitol, sorbitol, xylitol, fructose, sucrose, and calcium carbonate.

47. The method of claim 37, wherein the oral contraceptive agent comprises an estrogen and a progestin.

48. The method of claim 47, wherein the estrogen is selected from the group consisting of ethinyl estradiol, estradiol, estradiol valerate, and estradiol acetate, and the progestin is selected from the group consisting of norethindrone, norethindrone acetate, desogestrel, levonorgestrel, ethynodiol diacetate, norgestrel, norgestimate, gestodene, drospirenone, trimegestone, levodesogestrel, gestodyne, and nesterone.

49. The method of claim 48, wherein the carrier is selected from the group consisting of dicalcium phosphate, lactose, corn starch, microcrystalline cellulose, maltodextrin, dextrose, mannitol, sorbitol, xylitol, fructose, sucrose, and calcium carbonate.

50. The method of claim 49, wherein the tablets further comprise at least one of a flavor agent, a sweetener, and a color agent.

51. The method of claim 37, wherein each tablet weighs about 50 milligrams to about 300 milligrams.

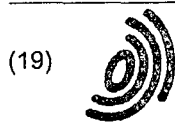
52. The method of claim 37, wherein the tablets have a hardness sufficient for blister packaging.

53. The method of claim 37, wherein the tablet has a hardness of about 5 kiloponds to about 15 kiloponds.

54. The method of claim 37, wherein the oral contraceptive agent comprises norethindrone and ethinyl estradiol, the carrier comprises dicalcium phosphate, lactose monohydrate, and maltodextrin, and the tablet further comprises sucralose, a flavor agent, sodium starch glycolate, povidone, and magnesium stearate.

55. The method of claim 37, wherein each tablet comprises a daily dosage of the oral contraceptive agent.

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(54) **Pharmaceutical combination of ethinylestradiol and drospirenone for use as a contraceptive**

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

In a specific embodiment, the composition consists of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 21 consecutive days, wherein said daily dosage units comprises the combination of drospirenone and ethinylestradiol. The composition may further comprise 7 or less daily dosage units containing no active agent or containing ethinylestradiol alone.

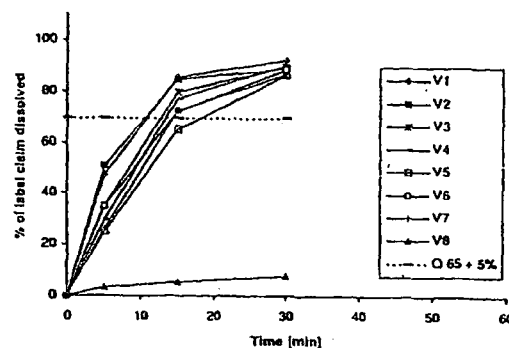


Fig. 1

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Description

FIELD OF THE INVENTION

[0001] The present invention relates to a pharmaceutical composition comprising drospirenone and ethinylestradiol, a method of providing dissolution of drospirenone, methods of inhibiting ovulation by administration of drospirenone and the use of drospirenone and ethinylestradiol for inhibiting ovulation.

BACKGROUND OF THE INVENTION

[0002] Oral contraceptives containing a combination of a gestagen and an estrogen component have been used since the 1960's. The earliest contraceptive preparations consisted of 21 tablets containing the combination of active agents and 7 tablets containing no active agent, and the amount of each active agent was the same in each tablet (the so-called one-phase preparations). Subsequently, preparations were developed that consisted of tablets containing different amounts and ratios of the active agents over the cycle of administration (the so-called multiple-phase preparations).

[0003] Contraceptive reliability is mainly provided by the gestagen component. The daily dosage should be at least the minimum of what is needed for the gestagen in question to inhibit ovulation effectively. The estrogen component acts to increase the ovulation inhibitory effect of gestagen and to ensure cycle stability. Since the introduction of oral contraceptives, the daily dosage of gestagen has been reduced through the development of new and more efficient gestagens than were present in the earlier contraceptive preparations. It has also been possible to reduce the daily dosage of estrogen.

[0004] 6 β ,7 β ;15 β ,16 β -dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone (drospirenone) is known from DE 26 52 761 in which its use as a diuretic compound is disclosed.

[0005] In DE 30 22 337, the gestagen-like activity of the compound and its consequent utility as a contraceptive agent is described at dosage levels of 0.5-50 mg of drospirenone per day. It is also noted that the mechanism of action of the compound is very similar to that of the natural corpus luteum hormone progesterone, and that it does not give rise to increased blood pressure for which reason it may be administered to women who have or are at risk of developing increased blood pressure. It is further described that drospirenone may be administered together with ethinylestradiol in an amount of 0.03-0.05 mg per day.

[0006] DE 30 51 166 discloses the use of the drospirenone for the treatment of gynaecological irregularities and for contraception at a dosage level of 0.5-50 mg per day.

[0007] EP 398 460 discloses the use of drospirenone for the treatment of androgen-induced disorders, aldosterone-induced disorders and hormonal irregularities as

well as for contraception at dosage levels of 0.5-50 mg, preferably 1-10 mg per day. Ethinylestradiol may be co-administered at a level of 0.02-0.04 mg per day.

[0008] US 5,756,490 discloses pharmaceutical combination preparations comprising 23 or 24 dosage units containing a combination of a gestagen and an estrogen and 4-10 dosage units containing estrogen alone. Drospirenone is mentioned as a possible, but not preferred, gestagenic compound and ethinylestradiol is mentioned as a possible, but not preferred, estrogenic compound.

SUMMARY OF THE INVENTION

[0009] In the course of research leading to the present invention, it has surprisingly been found that a hitherto undisclosed minimum dosage level of drospirenone is required for reliable contraceptive activity. Similarly, a preferred maximum dosage has been identified at which unpleasant side effects, in particular excessive diuresis, may substantially be avoided.

[0010] Accordingly, in a first aspect, the present invention relates to a pharmaceutical composition comprising, as a first active agent, 6 β ,7 β ;15 β ,16 β -dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone (drospirenone) in an amount corresponding to a daily dosage, on administration of the composition, of from about 2 mg to about 4 mg, and, as a second active agent, 17 α -ethinylestradiol (ethinylestradiol) in an amount corresponding to a daily dosage of from about 0.01 mg to about 0.05 mg, together with one or more pharmaceutically acceptable carriers or excipients.

[0011] Apart from the active substances themselves, it is envisaged that an ester or prodrug of drospirenone may be employed in the present composition, e.g. an oxyiminopregnane carbolactone as disclosed in WO 98/24801. Likewise, it is envisaged that esters or ethers of ethinylestradiol may be included in the composition.

[0012] In a further aspect, the invention relates to a method of inhibiting ovulation in a mammal, in particular a human, comprising administering, to said mammal, drospirenone in an amount in the range of from about 2 mg to about 4 mg of per day, together with ethinylestradiol in an amount of from about 0.01 mg to about 0.05 mg per day, said amounts being effective to inhibit ovulation in said mammal.

[0013] In a still further aspect, the invention relates to the use of drospirenone combined with ethinylestradiol for preparing a pharmaceutical preparation for the inhibition of ovulation in a mammal, in particular a human, the composition comprising an amount of drospirenone corresponding to a daily dosage, on administration of the composition, of from about 2 mg to about 4 mg, and comprising an amount of ethinylestradiol corresponding to a daily dosage, on administration of the composition, of from about 0.01 to about 0.05 mg.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] The invention is further described with reference to the drawings in which

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

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

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

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

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

DETAILED DISCLOSURE OF THE INVENTION

[0015] Drospirenone, which may be prepared substantially as described in, e.g., US 4,129,564 or WO 98/06738, is a sparingly soluble substance in water and aqueous buffers at various pH values. Furthermore, drospirenone is rearranged to an inactive isomer under acid conditions and hydrolysed under alkaline conditions. To ensure good bioavailability of the compound, it is therefore advantageously provided in a form that promotes rapid dissolution thereof.

[0016] It has surprisingly been found that when drospirenone is provided in micronized form (so that particles of the active substance have a surface area of more than 10,000 cm²/g, and the following particle size distribution as determined under the microscope: not more than 2 particles in a given batch with a diameter of more than 30 µm, and preferably ≤ 20 particles with a diameter of ≥ 10 µm and ≤ 30 µm) in a pharmaceutical composition, rapid dissolution of the active compound from the composition occurs in vitro ("rapid dissolution" is defined as the dissolution of at least 70% over about 30 minutes, in particular at least 80% over about 20 minutes, of drospirenone from a tablet preparation containing 3 mg of drospirenone in 900 ml of water at 37°C determined by the USP XXIII Paddle Method using a USP dissolution test apparatus 2 at 50 rpm). Instead of providing the drospirenone in micronized form, it is possible to dissolve it in a suitable solvent, e.g. methanol or ethyl acetate, and spray it onto the surface of inert carrier particles followed by incorporation of the particles containing dros-

pirenone on their surface in the composition.

[0017] Without wishing to be limited to any particular theory, it appears that the in vitro dissolution rate of drospirenone is connected to the dissolution rate in vivo resulting in rapid absorption of drospirenone in vivo on oral administration of the compound. This is an advantage because isomerization of the compound in the gastric environment and/or hydrolysis in the intestine is substantially reduced, leading to a high bioavailability of the compound.

[0018] With respect to ethinylestradiol which is also a sparingly soluble substance, though less sensitive to degradation than drospirenone under conditions prevailing in the gastrointestinal tract, it is also an advantage to provide it in micronized form or sprayed from a solution, e.g. in ethanol, onto the surface of inert carrier particles. This has the added advantage of facilitating a more homogenous distribution of the ethinylestradiol throughout the composition which might otherwise be difficult to obtain because ethinylestradiol is incorporated in extremely small amounts. When ethinylestradiol is provided in micronized form, it preferably has the following particle size distribution as determined under the microscope: 100% of the particles have a diameter of ≤ 15.0 µm, 99% of the particles have a diameter of ≤ 12.5 µm, 95% of the particles have a diameter of ≤ 10.0 µm, and 50% of the particles have a diameter of ≤ 3.0 µm. Furthermore, no particle is larger than 20 µm, and ≤ 10 particles have a diameter of ≥ 15 µm and ≤ 20 µm.

[0019] To obtain a more rapid rate of dissolution, it is preferred to include carriers or excipients which act to promote dissolution of both active substances. Examples of such carriers and excipients include substances that are readily soluble in water such as cellulose derivatives, carboxymethylcellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, gelled starch, gelatin or polyvinylpyrrolidone. In particular, it appears as though polyvinylpyrrolidone might be particularly helpful to promote dissolution.

[0020] The composition of the invention preferably comprises drospirenone in an amount corresponding to a daily dosage of from about 2.5 mg to about 3.5 mg, in particular about 3 mg. The amount of ethinylestradiol preferably corresponds to a daily dosage of from about 0.015 mg to about 0.04 mg, in particular from about 0.015 mg to about 0.03 mg. More particularly, the present composition comprises an amount of drospirenone corresponding to a daily dosage of from about 3.0 to about 3.5 mg and ethinylestradiol in an amount corresponding to from about 0.015 to about 0.03 mg.

[0021] Apart from its ability to inhibit ovulation, the composition of the invention has been found to possess pronounced anti-androgenic properties and may therefore be used in the prevention or treatment of androgen-induced disorders, in particular acne. Such use may be independent from or concomitant with the use as a contraceptive disclosed above. Furthermore, since drospirenone is an aldosterone antagonist, it has diuretic

Compared to the oral suspension, the relative bioavailability of drospirenone and ethinylestradiol from the tablets is 107% and 117%, respectively. It was therefore concluded that both drospirenone and ethinylestradiol are completely released from the tablets in vivo.

[0051] The absolute bioavailability of drospirenone was determined in two studies to be $76\% \pm 13\%$ after oral administration of 2 mg drospirenone to 8 young healthy women and $85\% \pm 24\%$ after oral administration of a microcrystalline suspension containing 3.13 mg drospirenone to 6 postmenopausal women.

[0052] The oral bioavailability of ethinylestradiol was determined in several studies, and mean values of from 36% to 59% were reported in the literature, indicating a first-pass effect.

Example 5

Contraceptive efficacy of formulations containing drospirenone and ethinylestradiol

[0053] An open-label, randomized trial with 52 female volunteers aged 20-35 years whose informed consent had been obtained included 1 pre-treatment cycle, 3 treatment cycles with two different tablet containing 2 mg and 3 mg drospirenone, respectively, but otherwise corresponding to the tablets prepared in Example 1, and a follow-up phase. A wash-out phase of 1 month preceded the treatment.

[0054] At defined time points, selected central and peripheral parameters were investigated: LH, FSH, 17β -estradiol, progesterone, cervical score, "spinnbarkeit", fern phenomenon. Ovarian function was checked by ultrasound. In addition, SHBG, CBG, prolactin, total testosterone, androstenedione, DHEA-S and selected metabolic parameters (serum glucose, triglycerides, cholesterol, HDL, LDL) were examined. Blood pressure, heart rate, body weight and cycle control were documented.

[0055] The results of the study showed that both LH and FSH were clearly suppressed with both trial preparations. Accordingly, the secretion of estradiol and progesterone were greatly reduced over all three treatment cycles with the exception of 3 volunteers receiving the 2 mg drospirenone preparation. This result was, in principle, confirmed by the accompanying ultrasound examinations. Follicular ripening occurred in several cases with both trial preparations. Although three ovulations were diagnosed with the preparation containing 2 mg drospirenone (one of which was described as "equivocal" and the other as a "tablet-taking error"), no differences were demonstrable statistically ($p > 0.05$) between the two trial preparations as regards the hormones LH, FSH, estradiol and progesterone, and the parameter "ovulation during the treatment cycles". In keeping with the hormones, cervical function was greatly limited and the "spinnbarkeit" and crystallisability of the cervical mucus was greatly reduced with both trial

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

[0056] The subjective and objective tolerance was good with both treatments. This was also the case for cycle control with the exception of the first cycle with 2 mg drospirenone. Blood pressure, heart rate and body weight remained constant in the majority of cases or showed a slight tendency to decrease.

After three months' treatment, it was concluded:

[0057] The two trial preparations were equally good as regards the subjective and objective tolerance.

[0058] No negative metabolic effects were observed with either preparation. HDL was influenced positively in the sense of an increase.

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

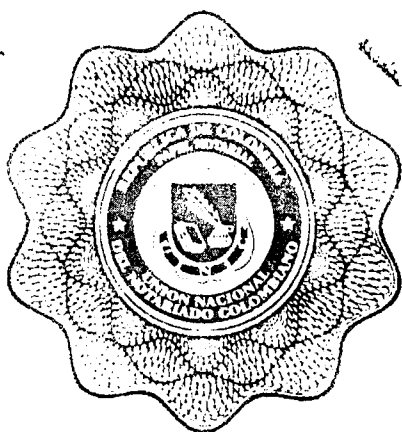
Claims

1. A pharmaceutical composition comprising, as a first active agent drospirenone in an amount corresponding to a daily dosage, on administration of the composition, of from about 2 mg to 4 mg, and as a second active agent, ethinylestradiol in an amount corresponding to a daily dosage of from about 0.01 mg to 0.05 mg, together with one or more pharmaceutically acceptable carriers or excipients, wherein said drospirenone has a surface area of more than $10\,000\text{ cm}^2/\text{g}$.
2. A pharmaceutical composition comprising, as a first active agent drospirenone in an amount corresponding to a daily dosage, on administration of the composition, of from about 2 mg to 4 mg, and as a second active agent, ethinylestradiol in an amount corresponding to a daily dosage of from about 0.01 mg to 0.05 mg, together with one or more pharmaceutically acceptable carriers or excipients, wherein at least 70% of said drospirenone is dissolved from said composition within 30 minutes, as determined by USP XXIII Paddle Method II using water at 37°C as the dissolution media and 50 rpm as the stirring rate.
3. The composition according to any one of claims 1 or 2, wherein drospirenone is sprayed from a solu-

- tion of drospirenone onto particles of an inert carrier.
4. The composition according to any one of claims 1 to 3, wherein the in vitro dissolution of ethinylestradiol is such that at least 70% is dissolved within 30 minutes, as determined by USP XXIII Paddle Method II using water at 37°C as the dissolution media and 50 rpm as the stirring rate. 5
 5. The composition according to any one of claims 1 to 4, wherein $\leq 20\%$ of the drospirenone is in the form of particles with a diameter of $\geq 10 \mu\text{m}$ and $\leq 30 \mu\text{m}$. 10
 6. A pharmaceutical preparation consisting of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 21 consecutive days, wherein said daily dosage units comprises a combination of drospirenone in an amount of from about 2 mg to 4 mg and ethinylestradiol in an amount from about 0.01 to 0.05 mg, wherein said drospirenone has a surface area of more than $10\,000 \text{ cm}^2/\text{g}$. 15 20
 7. A pharmaceutical preparation consisting of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 21 consecutive days, wherein said daily dosage units comprises a combination of drospirenone in an amount of from about 2 mg to 4 mg and ethinylestradiol in an amount from about 0.01 to 0.05 mg, wherein at least 70% of said drospirenone is dissolved from said dosage unit within 30 minutes, as determined by USP XXIII Paddle Method II using water at 37°C as the dissolution media and 50 rpm as the stirring rate. 25 30 35
 8. The preparation according to any one of claims 6 or 7, wherein the in vitro dissolution of ethinylestradiol is such that at least 70% is dissolved from said dosage unit within 30 minutes, as determined by USP XXIII Paddle Method II using water at 37°C as the dissolution media and 50 rpm as the stirring rate. 40 45
 9. The preparation according to any one of claims 6 to 8, wherein $\leq 20\%$ of the drospirenone is in the form of particles with a diameter of $\geq 10 \mu\text{m}$ and $\leq 30 \mu\text{m}$. 50
 10. The preparation according to any one of claims 6 to 9, which additionally comprises 7 or less daily dosage units containing no active agent intended for oral administration subsequent to the period of at least 21 consecutive days, the total number of daily dosage units being at least 28. 55
 11. The preparation according to any one of claims 6 to 9, wherein the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol is 21, 22, 23 or 24, and wherein the number of daily dosage units containing no active agent is 7, 6, 5 or 4.
 12. The preparation according to any one of claims 6 to 9 intended for oral administration for a period of at least 28 consecutive days, wherein at least 21 of said daily dosage units comprises a combination of drospirenone in an amount of from about 2 mg to 4 mg and ethinylestradiol in an amount from about 0.01 to 0.05 mg, and wherein 7 or less of said daily dosage units contain ethinylestradiol alone in an amount from about 0.01 to 0.05 mg.
 13. The preparation according to any one of claims 6 to 9, wherein the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol is 21, 22, 23 or 24, and wherein the number of daily dosage units comprising ethinylestradiol alone is 7, 6, 5 or 4.
 14. The preparation according to any one of claims 6 to 9, wherein the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol is 28, or a multiple of 28 such as 2-4, in particular 2 or 3, times 28.
 15. The preparation according to claim 7, wherein the number of daily dosage units intended for oral administration is for 2-4, preferably 2 or 3, times 28 consecutive days, followed by administration of the daily dosage units comprising the combination of drospirenone and ethinylestradiol for 21, 22, 23 or 24 consecutive days and subsequently administration of the daily dosage units containing no active agent, or administration of no daily dosage units, for 7, 6, 5 or 4 consecutive days.
 16. Use of drospirenone combined with ethinylestradiol for preparing a pharmaceutical composition for the inhibition of ovulation in a mammal, in particular a human, the composition comprising an amount of drospirenone corresponding to a daily dosage, on administration of the composition, of from about 2 mg to 4 mg, and comprising an amount of ethinylestradiol corresponding to a daily dosage, on administration of the composition, of from about 0.01 to 0.05 mg, and wherein said drospirenone has a surface area of more than $10\,000 \text{ cm}^2/\text{g}$.
 17. Use of drospirenone combined with ethinylestradiol for preparing a pharmaceutical composition for the inhibition of ovulation in a mammal, in particular a human, the composition comprising an amount of drospirenone corresponding to a daily dosage, on administration of the composition, of from about 2

mg to 4 mg, and comprising an amount of ethinylestradiol corresponding to a daily dosage, on administration of the composition, of from about 0.01 to 0.05 mg, wherein at least 70% of said drospirenone is dissolved from said composition within 30 minutes, as determined by USP XXIII Paddle Method II using water at 37°C as the dissolution media and 50 rpm as the stirring rate.

18. The use according to any one of claims 16 to 17, wherein $\leq 20\%$ of the drospirenone is in the form of particles with a diameter of $\geq 10 \mu\text{m}$ and $\leq 30 \mu\text{m}$.
19. The use according to any one of claims 16 to 18, wherein at least 70% of ethinyl estradiol is dissolved from the composition within 30 minutes, as determined by USP XXIII Paddle Method II using water at 37°C as the dissolution media and 50 rpm as the stirring rate.
20. Use of drospirenone combined with ethinylestradiol for preparing a pharmaceutical composition for the prevention or treatment of androgen-induced disorders in a female mammal, in particular a female human, the composition comprising an amount of drospirenone corresponding to a daily dosage, on administration of the composition, of from about 2 mg to 4 mg, and comprising an amount of ethinylestradiol corresponding to a daily dosage, on administration of the composition, of from about 0.01 to 0.05 mg, and wherein said drospirenone has a surface area of more than $10\,000 \text{ cm}^2/\text{g}$.
21. Use of drospirenone combined with ethinylestradiol for preparing a pharmaceutical composition for the prevention or treatment of androgen-induced disorders in a female mammal, in particular a female human, the composition comprising an amount of drospirenone corresponding to a daily dosage, on administration of the composition, of from about 2 mg to 4 mg, and comprising an amount of ethinylestradiol corresponding to a daily dosage, on administration of the composition, of from about 0.01 to 0.05 mg, wherein at least 70% of said drospirenone is dissolved from said composition within 30 minutes, as determined by USP XXIII Paddle Method II using water at 37°C as the dissolution media and 50 rpm as the stirring rate.
22. The use according to any one of claims 20 or 21, wherein the androgen-induced disorder is acne.
23. The use according to any one of claims 20 to 22, wherein $\leq 20\%$ of the drospirenone is in the form of particles with a diameter of $\geq 10 \mu\text{m}$ and $\leq 30 \mu\text{m}$.



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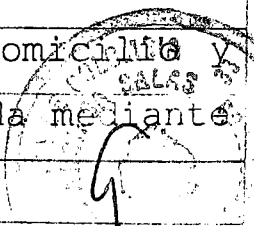
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REPUBLICA DE COLOMBIA
NOTARIA 33 DE BOGOTA D.C.
ESCRITURA PUBLICA NUMERO:1 6 5 8
- - MIL SEISCIENTOS CINCUENTA Y OCHO - -
FECHA DE OTORGAMIENTO: CUATRO (4) DE
JULIO - - - - -

DEL AÑO DOS MIL DOS (2002).
ACTO:
1.- PODER ESPECIAL.
OTORGADO POR: LAFRANCOL S.A., con Nit. No.
890.301.463-8
a favor de: JOSE LUIS REYES VILLAMIZAR, con C.C.No.
79.152.473 de Usaquén - Bogotá.
DIANA BEATRIZ LOPEZ
NOTARIA TREINTA Y TRES (33) DE BOGOTA D.C.
EN LA CIUDAD DE BOGOTA, DISTRITO CAPITAL,
DEPARTAMENTO DE CUNDINAMARCA, REPUBLICA DE COLOMBIA,
ANTE MI, DIANA BEATRIZ LOPEZ,
NOTARIA TREINTA Y TRES (33)
DE ESTE CIRCULO SE OTORGA LA ESCRITURA PUBLICA QUE
SE CONSIGNA EN LOS SIGUIENTES TERMINOS:
COMPARECIO: JUAN MARIA RENDON, mayor de edad,
vecino de Bogotá, D.C, identificado con la cédula de
ciudadanía número 17.125.100
Expedida en Bogotá
Y manifestó:
PRIMERO: Que obra en su carácter de representante
Legal de en nombre y representación de LAFRANCOL
S.A, sociedad comercial organizada y existente
conforme a las leyes colombianas, con domicilio y
sede principal en Cali - Valle, constituida mediante
escritura pública número

EL NOTARIO NO PUEDE AUTENTICAR LA COPIA POR TENER CORRESPONDENCIA CON LA FOTOCOPIA AUTENTICA QUE HA SIDO PRESENTADA.

24 SET 2007



De la Notaría

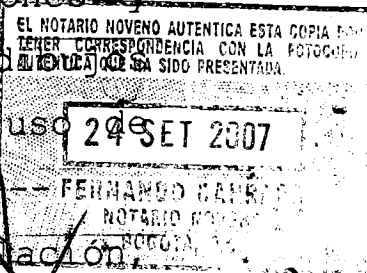
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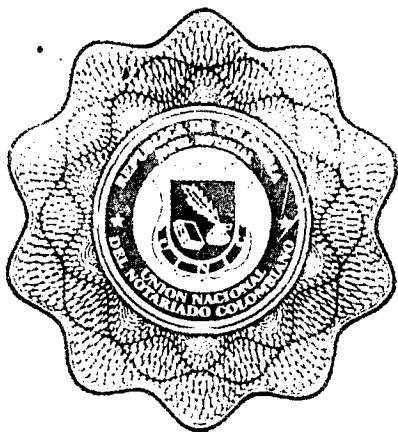
Reformada en distintas oportunidades, según consta en el certificado expedido por la Cámara de Comercio de Cali - Valle.-----

SEGUNDO: Que en tal carácter, por este público instrumento, concede PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE a **JOSE LUIS REYES VILLAMIZAR**, mayor de edad, vecino de Bogotá, D.C, identificado con la cédula de ciudadanía número 79.152.473 de Usaquén, abogado en ejercicio, portador de la T.P.No. 446 55 del C.S. de la J., domiciliado en Bogotá, D.C, República de Colombia, con dirección en la carrera 17 No. 88-23, Oficina 205, de la misma ciudad, como su representante con poder especial, amplio y suficiente, para obtener la protección los derechos de propiedad industrial y de libre competencia de Lafrancol S.A., a cuyo efecto lo autorizo, par que nos represente ante cualesquiera entidad o persona, ejerza o no jurisdicción, especialmente ante las el orden administrativo, contencioso, administrativo y judicial, en todo lo concerniente a los siguientes asuntos:-----

a.- Obtención, formulación de oberservaciones y oposición a patentes de invención, modelos y industriales y el registro de licencias de uso esos derechos.-----

b.- Las acciones de oposición, cancelación, nulidad, medidas cautelares, concesión de licencias y en general los procesos civiles, penales, administrativos o contencioso- administrativos relacionados con estos derechos u otros de diferente naturaleza, acciones y procesos que





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promueva Lafrancol S.A., o se promuevan contra esta y.-----

c.- Para que en todos los asuntos arriba determinados, tanto en los términos señalados por los artículos 42 y complementarios

de la decisión 486 de la Comunidad Andina como del artículo 70 del C.P.C. pueda sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar y ratificar los actos de agentes oficiosos y ceder a título gratuito y/o oneroso, licenciar, inscribir contratos de cesión y de licencia, inscripción de prendas, levantamiento de prendas, inscribir derechos de retención y en general todos los asuntos que se deban tramitar ante la Superintendencia de Industria y Comercio.-----

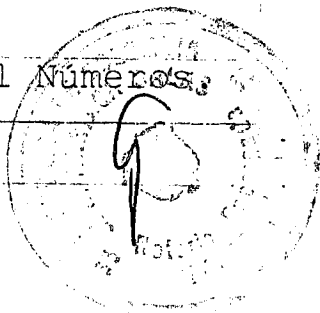
Manifestamos que de la veracidad de las declaraciones del contenido y autenticidad de los documentos anexos en éste instrumento público sólo respondemos los comparecientes.-

HASTA AQUI LA MINUTA PRESENTADA

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24 SET 2007
FERNANDO CA
NOTARIO NOVENO
BOGOTÁ, D.C.

OTORGAMIENTO Y AUTORIZACION: Leído el presente instrumento Público por los comparecientes y advertidos de la formalidad de su contenido, dentro del término legal, lo hallaron conforme con sus intenciones y lo aprobaron en todas sus partes y firmaron junto con la Suscrita Notaria quien da fe y lo autoriza. -----

Se utilizaron las hojas de papel Notarial Números AA 8567146, 8567152.



DERECHOS NOTARIALES: \$ 49.600.00

RESOLUCION No. 4188 del 28 de Diciembre del 2001

[Signature]
JUAN MARIA RENDON

C.C. No. 17.125.100 de Bogotá

LAFRANCOL S.A.

Nit. No. 890.301.463-8

TEL: 622-04-66.

ACEPTO :

[Signature]
JOSE LUIS REYES VILLAMIZAR

C.C. No. 79.152.473

TEL: 621-2631

[Signature]
DIANA BEATRIZ LOPEZ

DIANA BEATRIZ LOPEZ

NOTARIA 33 DE BOGOTA D.C.

n.c.a.

Es segunda COPIA (FOTOCOPIA)

tomada de su original que se expide conforme al

Artículo 79 del Decreto 960 de 1970 en 06

hojas útiles con destino a JOSE LUIS REYES

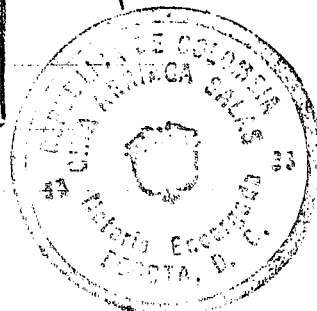
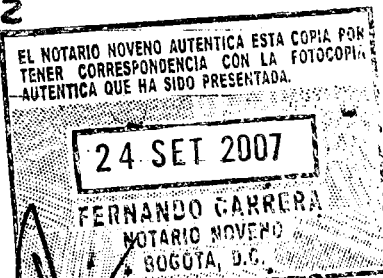
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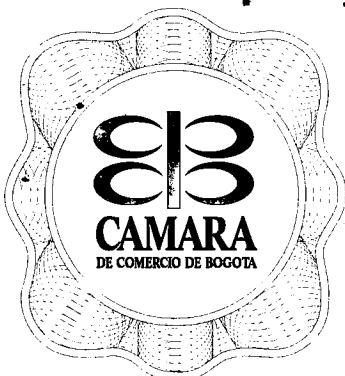
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05 JUL. 2002

[Signature]





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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070924

Hora Certificado 17:38:54

Operacion : 02CP20924074

PAGINA No. 1

null

CERTIFICA:

NOMBRE: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.

DOMICILIO: CALI VALLE

DIRECCION COMERCIAL : ---K 1 46 84

DIRECCION NOTIFICACION JUDICIAL: ---K 1 46 84

CIUDAD: CALI

MATRICULA MERCANTIL NRO. 5233-4 FECHA MATRICULA : 02 DE OCTUBRE DE 1958

DIRECCION ELECTRONICA : esperanzacortes@lafrancol.net

AFILIADO

CERTIFICA:

NIT : 890301463-8

CERTIFICA:

QUE POR ESCRITURA NRO. 1434 DEL 29 DE SEPTIEMBRE DE 1958 NOTARIA CUARTA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 02 DE OCTUBRE DE 1958 BAJO EL NRO. 18319 DEL LIBRO IX , SE CONSTITUYO LA SOCIEDAD DENOMINADA LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.

CERTIFICA:

REFORMAS

DOCUMENTO INS LIBRO	FECHA.DOC	ORIGEN	FECHA.INS	NRO.
E.P. 1104 19467	30/06/1959	NOTARIA CUARTA DE CALI	07/07/1959	
E.P. 2309 20089	26/12/1959	NOTARIA CUARTA DE CALI	29/12/1959	
E.P. 1725 24528	24/07/1962	NOTARIA CUARTA DE CALI	26/07/1962	
E.P. 1824 26360	31/07/1963	NOTARIA CUARTA DE CALI	14/08/1963	
E.P. 2422 26717	25/10/1963	NOTARIA CUARTA DE CALI	28/10/1963	
E.P. 1720	16/09/1964	NOTARIA CUARTA DE CALI	22/09/1964	

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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PAGINA No. 2

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2975 IX			
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E.P. 6241	27/12/2006	NOTARIA TERCERA DE CALI	19/01/2007
625 IX			

CERTIFICA:

VIGENCIA: 29 DE SEPTIEMBRE DEL AÑO 2057

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070924

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Operacion : 02CP20924074

PAGINA No. 3

CERTIFICA:

OBJETO SOCIAL. SE OCUPA EN: A) FABRICACION, DISTRIBUCION Y VENTA EN EL TERRITORIO DE LA REPUBLICA DE COLOMBIA O EN EL EXTRANJERO DE CUALESQUIERA TIPOS DE VACUNAS, PRODUCTOS QUIMICOS, FARMACEUTICOS ALIMENTICIOS FUNCIONALES, COSMETICOS Y FISIOLOGICOS, REACTIVOS, ANTIBIOTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS DIETETICOS, COLORANTES DE PERFUMERIA Y AFINES. B) LA REPRESENTACION DE CASAS FABRICANTES NACIONALES O EXTRANJERAS DE ESTOS MISMOS PRODUCTOS. C) FABRICACION, IMPORTACION, DISTRIBUCION Y VENTA DE CUALESQUIERA TIPOS DE PRODUCTOS VETERINARIOS. D) LA REALIZACION DE TODOS LOS ACTOS, CONTRATOS, CONVENIOS, DIRECTAMENTE RELACIONADOS CON LOS FINES ANTES INDICADOS. EN DESARROLLO DE SU OBJETO SOCIAL PODRA LA SOCIEDAD ADQUIRIR Y VENDER BIENES RAICES Y MUEBLES, DARLOS Y TOMARLOS EN ARRENDAMIENTO, GARANTIZAR CON HIPOTECA SOBRE LOS BIENES RAICES O CON PRENDA SOBRE LOS BIENES MUEBLES, OBLIGACIONES A CARGO DE LA SOCIEDAD; DAR Y RECIBIR A MUTUO COMERCIAL DINERO Y CELEBRAR LOS CONTRATOS COMERCIALES DE CAMBIO EN TODAS SUS MANIFESTACIONES, FUNDAR EMPRESAS QUE TENGAN LA MISMA FINALIDAD SOCIAL O ASOCIARSE CON ELLAS.

CERTIFICA:

ORGANOS DE DIRECCION Y ADMINISTRACION: 1) ASAMBLEA GENERAL DE ACCIONISTAS; 2) JUNTA DIRECTIVA; 3) GERENCIA GENERAL. TAMBIEN TENDRA UN REVISOR FISCAL.

ADMINISTRACION: LA ADMINISTRACION INMEDIATA DE LA SOCIEDAD, SU REPRESENTACION LEGAL Y LA GESTION DE LOS NEGOCIOS SOCIALES ESTARAN A CARGO DE UN GERENTE, DESIGNADO POR LA ASAMBLEA GENERAL DE ACCIONISTAS, PARA PERIODOS DE DE DOS (2) AÑOS REELEGIBLE INDEFINIDAMENTE Y REMOVIBLE LIBREMENTE POR ELLA EN CUALQUIER TIEMPO.

PARAGRAFO PRIMERO. SUPLENTE: EL GERENTE Y REPRESENTANTE LEGAL TENDRA LOS SIGUIENTES SUPLENTE: PRIMERO, SEGUNDO Y TERCERO QUE LO REEMPLAZARAN EN LOS CASOS DE AUSENCIAS ACCIDENTAL, TEMPORAL Y ABSOLUTA CON LAS LIMITACIONES QUE MAS ADELANTE SE ESTABLECEN.

PARAGRAFO SEGUNDO. EL TERCER SUPLENTE DEL GERENTE GENERAL Y REPRESENTANTE LEGAL ESTARA LIMITADO EN SUS FUNCIONES A: COMPROMETER LOS NEGOCIOS SOCIALES EN CUANTIA NO SUPERIOR A CUATRO MIL DOSCIENTOS SALARIOS MINIMOS MENSUALES LEGALES VIGENTES (4.200 SMMMLV); CELEBRAR CONTRATOS COMERCIALES DE COMPRAVENTA EN GENERAL YA SEA CON LA NACION (MINISTERIOS Y DEPARTAMENTOS ADMINISTRATIVOS), ENTIDADES DESCENTRALIZADAS (ESTABLECIMIENTOS PUBLICOS, EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMIA MIXTA), EMPRESAS SOCIALES CIVILES Y COMERCIALES, CUALQUIERA QUE SEA SU NATURALEZA CON FACULTADES PARA EXIGIR O SUSCRIBIR LOS DOCUMENTOS Y GARANTIAS NECESARIOS HASTA LA CUANTIA ANTES MENCIONADA.

FUNCIONES DEL GERENTE: A) ... B) EJECUTAR Y HACER CUMPLIR LOS ACUERDOS Y

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070924

Hora Certificado 17:38:54

Operacion : 02CP20924074

PAGINA No. 4

DECISIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS Y DE LA JUNTA DIRECTIVA Y HACER USO DE LA RAZON SOCIAL. C) REPRESENTAR LEGALMENTE A LA SOCIEDAD CONFORME A LA LEY ANTE TODAS LAS AUTORIDADES CIVILES, JUDICIALES, MILITARES, SANITARIAS, DE POLICIA, ADUANALES, POSTALES, ETC. G) LLEVAR A CABO LA GESTION COMERCIAL Y FINANCIERA. H) TENDRA LA PLENA RESPONSABILIDAD DE LA ACCION ADMINISTRATIVA, LA COORDINACION Y LA SUPERVISION GENERAL DE LA SOCIEDAD, LAS CUALES CUMPLIRA CON ARREGLO A LAS NORMAS DE LOS ESTATUTOS.

EN EL EJERCICIO DE SUS FUNCIONES, EL GERENTE PUEDE: 1.- COMPARECER EN LOS JUICIOS, TRANSIGIR Y COMPROMETER LOS NEGOCIOS SOCIALES DE CUALQUIERA NATURALEZA QUE FUEREN, INTERPONER TODO GENERO DE RECURSOS Y CONSTITUIR APODERADOS QUE LO REPRESENTEN JUDICIAL O EXTRAJUDICIALMENTE. 2.- ENAJENAR A CUALQUIER TITULO Y COMPRAR BIENES MUEBLES, CELEBRAR CONTRATOS COMERCIALES DE COMPRA Y VENTA EN GENERAL YA SEA CON LA NACION (MINISTERIOS Y DEPARTAMENTOS ADMINISTRATIVOS), ENTIDADES DESCENTRALIZADAS (ESTABLECIMIENTOS PUBLICOS), EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMIA MIXTA), EMPRESAS O SOCIEDADES CIVILES Y COMERCIALES CUALQUIERA QUE SEA SU NATURALEZA Y SU CUANTIA, CON AMPLIAS FACULTADES QUE EXIGIR O SUSCRIBIR LOS DOCUMENTOS, Y GARANTIAS NECESARIAS. CONTRATAR PRESTAMOS CUALQUIERA QUE SEA SU CUANTIA, CELEBRAR EL CONTRATO COMERCIAL DE MUTUO EN TODAS SUS MANIFESTACIONES Y SUSCRIBIR LOS DOCUMENTOS Y COMPROMISOS RESPECTIVOS. HACER DEPOSITOS EN BANCOS Y AGENCIAS BANCARIAS, FIRMAR CHEQUES, LETRAS, PAGARES, GIROS, LIBRANZAS Y CUALQUIER OTRO DOCUMENTO, ASI COMO NEGOCIAR ESTOS INSTRUMENTOS, TENERLOS, COBRARLOS, PAGARLOS, DESCARGARLOS, ETC.

CERTIFICA:

DOCUMENTO: ACTA No. 99 DEL 14 DE MARZO DE 2002

ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS

INSCRIPCION: 09 DE SEPTIEMBRE DE 2002 No. 14675 DEL LIBRO IX

FUE (RON) NOMBRADO (S) :

GERENTE GENERAL Y REPRESENTANTE LEGAL

JUAN MARIA RENDON GUTIERREZ

C.C.17125100

PRIMER SUPLENTE DEL GERENTE

ESTHER ISABEL VENTURA DE RENDON

C.C.38979831

SEGUNDO SUPLENTE DEL GERENTE

ROBERTO M. VENTURA CRISPINO

C.C.9086003

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263
263

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070924

Hora Certificado 17:38:54

Operacion : 02CP20924074

PAGINA No. 5

PRESIDENTE

ESTHER ISABEL VENTURA DE RENDON
C.C.38979831

VICEPRESIDENTE

ROBERTO S. VENTURA PAULY
C.C.16697614

CERTIFICA:

DOCUMENTO: ACTA No. 105 DEL 09 DE NOVIEMBRE DE 2004
ORIGEN: ASAMBLEA DE ACCIONISTAS
INSCRIPCION: 17 DE FEBRERO DE 2005 No. 2032 DEL LIBRO IX

FUE (RON) NOMBRADO(S) :

TERCER SUPLENTE DEL GERENTE
JUAN PABLO REYES VILLAMIZAR
C.C.80419709

CERTIFICA:

DOCUMENTO: ACTA No. 99 DEL 14 DE MARZO DE 2002
ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS
INSCRIPCION: 09 DE SEPTIEMBRE DE 2002 No. 14675 DEL LIBRO IX

DOCUMENTO: ACTA No. 105 DEL 09 DE NOVIEMBRE DE 2004
ORIGEN: ASAMBLEA DE ACCIONISTAS
INSCRIPCION: 17 DE FEBRERO DE 2005 No. 2031 DEL LIBRO IX

FUE (RON) _NOMBRADO(S)

JUNTA DIRECTIVA

PRINCIPALES

PRIMER RENGLON
ESTHER ISABEL VENTURA DE RENDON
C.C.38979831

SEGUNDO RENGLON

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070924 Hora Certificado 17:38:54

Operacion : 02CP20924074 PAGINA No. 6

ROSA VICTORIA VENTURA DE VISBAL
C.C.38992048

TERCER RENGLON
JUAN PABLO REYES VILLAMIZAR
C.C.80419709

SUPLENTES

PRIMER RENGLON
JUAN MARIA RENDON GUTIERREZ
C.C.17125100

SEGUNDO RENGLON
ROBERTO M. VENTURA CRISPINO
C.C.9086003

TERCER RENGLON
ROBERTO S. VENTURA PAULY
C.C.16697614

CERTIFICA:

DOCUMENTO: ACTA No. 99 DEL 14 DE MARZO DE 2002
ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS
INSCRIPCION: 09 DE SEPTIEMBRE DE 2002 No. 14675 DEL LIBRO IX

FUE (RON) NOMBRADO(S) :

REVISOR FISCAL
ALFREDO LOPEZ & CIA. LTDA
NIT.800026893-5

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 20 DE OCTUBRE DE 2006
ORIGEN: ALFREDO LOPEZ & CIA LTDA
INSCRIPCION: 07 DE NOVIEMBRE DE 2006 No. 12672 DEL LIBRO IX

FUE (RON) NOMBRADO(S) :

REVISOR FISCAL PRINCIPAL
ALFREDO LOPEZ CAMPO

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264
264

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070924

Hora Certificado 17:38:54

Operacion : 02CP20924074

PAGINA No. 7

C.C.8241912

REVISOR FISCAL SUPLENTE
GEOVANA GONZALEZ GALINDO
C.C.66959852

CERTIFICA:

CAPITAL AUTORIZADO: \$7,500,000,000
NUMERO DE ACCIONES: 750,000,000
VALOR NOMINAL: \$10
CAPITAL SUSCRITO: \$6,000,000,000
NUMERO DE ACCIONES: 600,000,000
VALOR NOMINAL: \$10
CAPITAL PAGADO: \$6,000,000,000
NUMERO DE ACCIONES: 600,000,000
VALOR NOMINAL: \$10

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.5234- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL
UBICADO EN: ---K 1 46 84 DE CALI
RENOVO : POR EL A?O 2007

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.369809- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL S A
UBICADO EN: --K 1 46A 70 DE CALI
FECHA MATRICULA : 29 DE ABRIL DE 1994
RENOVO : POR EL A?O 2007

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070924

Hora Certificado 17:38:54

Operacion : 02CP20924074

PAGINA No. 8

EL NRO.369810- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL S A

UBICADO EN: ---K 1A 46 A 32 DE CALI

FECHA MATRICULA : 29 DE ABRIL DE 1994

RENOVO : POR EL AÑO 2007

CERTIFICA:

QUE LA SOCIEDAD EFECTUO LA RENOVACION DE SU MATRICULA MERCANTIL EL 29 DE
MARZO DE 2007 .

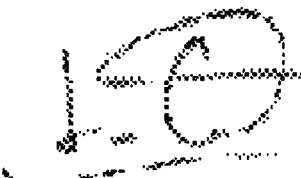
CERTIFICA:

QUE NO FIGURAN OTRAS INSCRIPCIONES QUE MODIFIQUEN TOTAL O PARCIALMENTE EL
PRESENTE CERTIFICADO.

LOS ACTOS Y DOCUMENTOS REGISTRADOS QUEDAN EN FIRME CINCO (5) DIAS HABILES
DESPUES DE LA FECHA DE SU INSCRIPCION, SIEMPRE Y CUANDO DENTRO DE DICHO
TERMINO NO SEAN OBJETO DE RECURSOS EN LA VIA GUBERNATIVA.

DE CONFORMIDAD CON EL DECRETO 2150 DE 1.995 Y LA AUTORIZACION IMPARTIDA POR
LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO LA FIRMA MECANICA QUE APARECE A
CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES.

DADO EN CALI A LOS 24 DIAS DEL MES DE SEPTIEMBRE DEL AÑO 2007 HORA: 05:16:15



88
265

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

BO OFICIAL DE CAJA : 07 - 78,570
A : SEPTIEMBRE 27 DE 2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No 05-130115- -00007-0000

Fecha: 2007-09-27 16:41:37 Dep: 2020 NUECREACIONE
Tra: 2 PATENTES Eve: 1 REGDEPOSITO
Act: 400 OPUS/OBSERVTER Folios: 89

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	69812082	27/09/2007	2,048,000.00

***** CONCEPTO *****

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

SON: DOSCIENTOS CINCUENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

8/9
266
266

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 78,582
FECHA : SEPTIEMBRE 27 DE 2007

Fecha: 2007-09-27 16:41:37 Dep: 2020 NUECREACIONE
Tpe: 2 PATENTES Ave: 1 REGDEPOSITO
Act: 400 CROSOBSERVTER Folios: 89

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	69812084	27/09/2007	576,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-08	PRORROGA DE TERMINOS	72,000.00
TOTAL :			\$ 72,000.00

SON: SETENTA Y DOS MIL PESOS

RESPONSABLE : _____

[Handwritten Signature]