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Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 06-120228- -00006-0000
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FORMULARIO UNICO DE OPOSICION
2000-12

1 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		

2 SOLICITUD PUBLICADA

Número del expediente: 06 120.228
Solicitante: SCHERING AKTIENGESELLSCHAFT.
Apoderado: J. IAN RAISBECK
Título de la nueva creación o denominación del signo:
"TRATAMIENTO DE LA HEMORRAGIA DE DISRUPCIÓN EN REGÍMENES ANTICONCEPTIVOS EXTENDIDOS."
GACETA No. 582 de 30 de noviembre de 2007,
N° de publicación: 981

3 OPOSICION PRESENTADA POR:

OPOSITOR	Nombre: **Lafrancol S.A.** Dirección: **Carrera 1 No. 45-84** Teléfono: **(092) 449.30.51** Fax: Domicilio: **Cali – Valle**	IDENTIFICACION C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Número: **890 301 463 -8**
REPRESENTANTE O APODERADO (74)	Nombre: **José Luis Reyes Villamizar** Dirección: **Cra. 17 No. 88-23, Of. 205** Teléfono: **621.26.31** E-mail: **info@reyes-abogados.com** Fax: **621.25.42** Domicilio: **Bogotá, D.C.**	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: **79'152.473 de Usaquén** **TP 44655**

4 **FUNDAMENTOS DE LA OPOSICION:**

Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000). Se violan los artículos 14, (las patentes de invención deben ser nuevas, tener nivel inventivo y ser suceptibles de aplicación industrial), 16, 18 (una invención tiene nivel inventivo si no es obvia para una persona versada en la materia) 20-d (los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales).

Justificación: VER ANEXO

5 **Comprobante de pago No.** 08-17.090 (Oposición) **Fecha** Febrero 27 de 2008
(Prórroga) Fecha

6 **Anexos:**

- [x] Comprobante de pago de la tasa
- [x] Poderes, si fuere el caso
- [x] Pruebas de los fundamentos de la oposición
- [x] Certificado de existencia y representación legal de las partes, cuando sean personas jurídicas
- [ ] Documentos que acrediten el legítimo interés, si fuere el caso
- [x] 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

REYES & REYES
ABOGADOS

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Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
E. S. D.

REF: **Expediente 06 120.228**

TÍTULO SOLICITADO: **"TRATAMIENTO DE LA HEMORRAGIA DE DISRUPCIÓN EN REGÍMENES ANTICONCEPTIVOS EXTENDIDOS."**

PUBLICACIÓN: **Gaceta 582 de 30 de Noviembre de 2007, número de publicación 981.**

PRIORIDAD: **US 60/566.443 de 30/04/2004**
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US 60/577.199 de 07/06/2004
US 60/638.380 de 27/12/2004
US 60/660.068 de 10/03/2005

SOLICITANTE: **SCHERING AKTIENGESELLSCHAFT**

APODERADO: **J. IAN RAISBECK**

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, actuando como agente oficioso, en nombre de la sociedad **LABORATORIO FRANCO-COLOMBIANO, LAFRANCOL S.A.**, de conformidad con la caución prestada, y estando dentro del plazo establecido por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito formular la siguiente:

I. PETICIÓN

Negar el beneficio patentario a la solicitud contenida en el expediente **06-120-228,** por no cumplir con los requisitos de patentabilidad a que se refieren los artículos 14, 16, 18 y 20 literal d) 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 **LABORATORIO FRANCO COLOMBIANO S.A. – LAFRANCOL S.A.** legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría, en forma contraria al Régimen Común Andino de Propiedad Industrial, el empleo de ciertas sustancias y composiciones farmacéuticas, en detrimento de sus legítimos intereses comerciales y de la libre competencia.

III. FUNDAMENTOS DE LA OPOSICIÓN

La solicitud colombiana en trámite, referida a un método para anticoncepción que comprende la administración monofásica continua de una preparación activa que contiene un estrógeno (etinil estradiol o estradiol) y un progestágeno, el cual incluye un primer periodo de toma, un segundo periodo de suspensión de la toma y un tercer periodo de retoma, y que es útil para moderar problemas de hemorragias relacionadas con el uso extendido de anticonceptivos hormonales; incumple con los requisitos indispensables para otorgársele el privilegio de patente de invención, tal y como se demuestra con los siguientes argumentos:

3.1. Existe suficiente información de carácter científico que revela los aspectos contenidos por la solicitud colombiana en trámite, tales como la combinación de estrógenos y progestanos en regimenes monofásicos y cantidades que permitan disminuir ciertos efectos adversos, como las hemorragias y afecciones andrógenas; información que demuestra evidente que lo contenido en el capítulo reivindicatorio de dicha solicitud colombiana en tramite, carece por completo de nivel inventivo, veamos:

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- **Use Of An Oral Contraceptive Containing Drospirenone In An Extended Regimen[1].**

  Abstract: As well as providing reliable contraception, modern low-dose oral contraceptives may offer some non-contraceptive advantages. Positive effects on problems such as edema with weight increase and breast tenderness, bloating, dysmenorrhea, and an improvement in skin and hair condition have been reported in several studies using an oral contraceptive containing drospirenone. If these disorders are cycle-dependent, use of the contraceptive in an extended regimen may be of additional benefit. The study reported in this paper followed 1433 women, 175 of whomtook the drospirenone-containing pill continuously for between 42 and 126 days. Some symptoms of the premenstrual syndrome were influenced very satisfactorily by administration in an extended regimen.

- **Attitude Of German Women And Gynecologists Towards Long-Cycle Treatment With Oral Contraceptives[2].**

  Abstract: Long-cycle regimens with continuous use of oral contraceptives (OCs) for 3 or 6 months followed by a hormone-free interval of 7 days may reduce or prevent cycle-dependent and menses-related complaints. A representative survey carried out with 1195 German women in different agegroups revealed that only 26-35% of the women aged between 15 and 49 years preferred monthly bleeding, while 37-46% wished to never bleed. The reasons for the refusal of regular menstruations were fewer severe menstrual complaints, better hygiene, higher quality of life, and less blood loss. Among the women who preferred regular withdrawal bleeding during the use of OCs, the main reasons were fear of pregnancy, infertility and adverse effects, and that menstruations were natural. Between 32% and 54% of the women would suppress menstruation sporadically and 11-14% for a longer period of time. After continuous treatment with a combination of 30 microg ethinyl estradiol and 2 mg dienogest for 6 months, the majority of women preferred the long-cycle regimen as compared to the conventional OC regimen despite a higher rate of irregular bleeding. Bleeding occurred primarily in first-time users of OC, particularly during the administration of the second OC pack. A survey carried out with German gynecologists revealed that most physicians prescribed extended OC cycles primarily for medical reasons, e.g., dysmenorrhea, hypermenorrhea, endometriosis and premenstrual dysphoric disorder. The gynecologists preferred a regimen with three packs of extended use of OCs.

- **An Open-Label, Multicenter, Noncomparative Safety And Efficacy Study Of Mircette, A Low-Dose Estrogen-Progestin Oral Contraceptive. The Mircette Study Group[3].**

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[1] Use of an oral contraceptive containing drospirenone in an extended regimen. (eng; includes abstract) By Sillem M, The European Journal Of Contraception & Reproductive Health Care: The Official Journal Of The European Society Of Contraception [Eur J Contracept Reprod Health Care], 2003 Sep; Vol. 8 (3), pp. 162-9; PMID: 14667328.

[2] Attitude of German women and gynecologists towards long-cycle treatment with oral contraceptives. By: Wiegratz, I.; Hommel, H.H.; Zimmermann, T.; Kuhl, H.. Contraception, Jan2004, Vol. 69 Issue 1, p37, 6p; DOI: 10.1016/j.contraception.2003.09.004; (AN 11885388)

[3] An open-label, multicenter, noncomparative safety and efficacy study of Mircette, a low-dose estrogen-progestin oral contraceptive. The Mircette Study Group. (eng; includes abstract), American Journal Of Obstetrics And Gynecology [Am J Obstet Gynecol], 1998 Jul; Vol. 179 (1), pp. S2-8; PMID: 9704812.

OBJECTIVE: The primary efficacy and safety of Mircette (brand of desogestrel/ethinyl estradiol and ethinyl estradiol), an oral contraceptive containing 150 microg desogestrel and microg ethinyl estradiol given for 21 days, followed by 2 days of placebo and then 5 days 10 microg ethinyl estradiol, was evaluated. STUDY DESIGN: In a large, open-label, 18-month, multicenter trial, a total of 1143 of 1250 healthy female subjects contributed to the determination of extent of exposure, for an equivalent of 1080.8 woman-years of use. RESULTS: Absence of withdrawal bleeding occurred in 5.5% of total cycles and intermenstrual bleeding occurred in 12.0% of total cycles. Breakthrough spotting was more common than breakthrough bleeding. The Pearl Index for total pregnancies during treatment was 1.02/100 woman-years. Fewer than 3% of subjects discontinued study participation, primarily because of menstrual problems, indicating that Mircette was an oral contraceptive acceptable to the women studied. Overall 73.6% of all subjects reported one or more adverse events, and a total of 43.9% of subjects reported drug-related adverse events. The most common drug-related adverse events reported included headache (8.5%), breast pain (7.3%), dysmenorrhea (4.2%), and menstrual disorder (4.2%). There were no reports of venous thromboembolic events or of significant changes in blood pressure, lipid metabolism, or serum glucose level. CONCLUSION: The study confirmed that Mircette is a safe and efficacious oral contraceptive that is well tolerated and acceptable to women who have previously used oral contraceptives, as well as first-time users.

- **Selectivity and minimal androgenicity of norgestimate in monophasic and triphasic oral contraceptives[4].**

Abstract: *The contraceptive progestin norgestimate (NGM) has a high affinity for uterine progestin receptors and a lack of affinity for androgen receptors similar to that of natural progesterone. NGM's selectivity results in excellent efficacy, cycle control, and minimal androgenicity when it is combined with ethinyl estradiol (EE). Clinical studies of a monophasic regimen of NGM/EE indicate a positive impact on lipid metabolism, revealing an increase in serum levels of high-density lipoprotein cholesterol with a concomitant and significant decrease in the low-density lipoprotein/high-density lipoprotein cholesterol ratio. Little impact on carbohydrate metabolism was noted. Serum levels of sex hormone binding globulin, an indicator of androgen-estrogen balance, also increased significantly with NGM/EE in accordance with its low androgenic activity. A significant between-regimen difference in SHBG was seen in a comparison study of NGM/EE and LNG/EE triphasic formulations (a mean rise of 68.6% with NGM/EE vs a decrease of 6.1% with LNG/EE). NGM's lack of estrogenicity was evidenced by unchanged prolactin levels and absence of effect on the coagulation system. In a large study of the monophasic formulation in 59,701 women, some improvement in acne was reported as well as minimal weight gain. An overview of clinical data is provided from United States and European trials as well as some preclinical data relevant to NGM's selectivity.*

3.2. La publicación internacional WO 02/22110 publicada el 21 de Marzo de 02 y titulada "CONTRACEPTION PROCESS AND ADMINISTRATION FORM FOR THE SAME" revela:

[4] Selectivity and minimal androgenicity of norgestimate in monophasic and triphasic oral contraceptives. (eng; includes abstract) By Anderson FD, Acta Obstetricia Et Gynecologica Scandinavica. Supplement [Acta Obstet Gynecol Scand Suppl], 1992; Vol. 156, pp. 15-21; PMID: 1324552

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Process for hormonal contraception, in which in a plurality of substantially time-unlimited, linked taking periods and optionally having a sequence lasting several years and which in each case comprise at least one taking cycle with a duration-constant taking phase lasting several days within the particular taking period and a taking pause lasting several days, in which taking phase or phases per day administration takes place of a daily unit with at least one contraceptively acting hormone component, such as estrogen and/or gestagen, and in the taking pause or pauses administration takes place either of placebos free from any hormone component or the particular taking pause remains entirely administration-free and the duration of the taking phase or phases of at least the final taking period lasts at least 22 days, as well as an administration form for hormonal contraception, particularly for performing the aforementioned process, with a plurality of packaging units, which in each case have at least one set of daily units to be administered within a taking cycle of a taking period, within which the duration of the taking phases is constant and comprising in each case one taking phase and a neighbouring taking pause and which in each case comprise at least one number of hormone daily units corresponding to the duration of the taking phase or phases, in each case with a content of at least one contraceptively acting hormone component, such as estrogen and/or gestagen, as well as a number of placebos corresponding to the duration of the taking pause or pauses and the duration of the taking phase or phases of at least the last of the taking periods following the first taking period amounts to at least 22 days.

(...)

It is also possible for the hormone daily units to in each case incorporate 0.5 to 3 mg inclusive of chlormadinone acetate, 1 to 3 mg inclusive of cyproterone acetate, 0.05 to 0.2 mg inclusive of desogestrel, 1 to 3 mg inclusive of dienogest, 0.035 to 0.1 mg inclusive of gestoden, 0.025 to 0.5 mg inclusive of levonorgestrel, 0.25 to 3 mg inclusive of lynestrenol, 75 to 200 mg inclusive of medroxyprogesterone acetate, 0.175 to 1.5 mg inclusive of norethisterone, 0.1 to 0.3 mg inclusive or norgestimate, 0.015 to 0.75 mg inclusive of norgestrel, 0.25 to 3 mg inclusive of norethisterone acetate, 100 to 300 mg inclusive of norestisterone enanthate, 1.5 to 4 mg inclusive of drosperinone, 10 to 50 µg inclusive of ethinylestradiol, 25 to 50 µg inclusive of mestranol and/or 0.25 to 6 mg inclusive of estradiol (as a representative of natural estrogen).

(...)

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

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

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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Published:
— *without international search report and to be republished upon receipt of that report*

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

WO 02/22110 A2

(54) Title: CONTRACEPTION PROCESS AND ADMINISTRATION FORM FOR THE SAME

(57) Abstract: Process for hormonal contraception, in which in a plurality of substantially time-unlimited, linked taking periods and optionally having a sequence lasting several years and which in each case comprise at least one taking cycle with a duration-constant taking phase lasting several days within the particular taking period and a taking pause lasting several days, in which taking phase or phases per day administration takes place of a daily unit with at least one contraceptively acting hormone component, such as estrogen and/or gestagen, and in the taking pause or pauses administration takes place either of placebos free from any hormone component or the particular taking pause remains entirely administration-free and the duration of the taking phase or phases of at least the final taking period last at least 22 days, characterized in that the duration of the taking phase or phases in any taking period preceding a following taking period is shorter than in each case following taking period, as well as administration form for hormonal contraception and in particular for the performance thereof.

CONTRACEPTION PROCESS AND ADMINISTRATION FORM FOR THE SAME

Process for hormonal contraception, in which in a plurality of substantially time-unlimited, linked taking periods and optionally having a sequence lasting several years and which in each case comprise at least one taking cycle with a duration-constant taking phase lasting several days within the particular taking period and a taking pause lasting several days, in which taking phase or phases per day administration takes place of a daily unit with at least one contraceptively acting hormone component, such as estrogen and/or gestagen, and in the taking pause or pauses administration takes place either of placebos free from any hormone component or the particular taking pause remains entirely administration-free and the duration of the taking phase or phases of at least the final taking period lasts at least 22 days, as well as an administration form for hormonal contraception, particularly for performing the aforementioned process, with a plurality of packaging units, which in each case have at least one set of daily units to be administered within a taking cycle of a taking period, within which the duration of the taking phases is constant and comprising in each case one taking phase and a neighbouring taking pause and which in each case comprise at least one number of hormone daily units corresponding to the duration of the taking phase or phases, in each case with a content of at least one contraceptively acting hormone component, such as estrogen and/or gestagen, as well as a number of placebos corresponding to the duration of the taking pause or pauses and the duration of the taking phase or phases of at least the last of the taking periods following the first taking period amounts to at least 22 days.

Oral contraceptives are typically taken for a 21 day period. This taking phase generally follows a 7 day taking pause leading to menstruation (withdrawal bleeding). This taking regimen was developed in around 1960 because it largely corresponds to the natural cycle, but there is no medical reason for this.

The administration form according to the invention can also be characterized in that the number of hormone daily units per taking phase of the packaging unit corresponding to the last taking period is at least 60.

It is possible for the number of hormone daily units per taking phase of the packaging unit corresponding to the final taking period to be at least 70.

The invention also proposes that the number of hormone daily units per taking phase of the packaging unit corresponding to the last taking period is at least 80.

It is possible for the number of hormone daily units per taking phase of the packaging unit corresponding to the final taking period to be at least 90.

It is also possible for the number of hormone daily units per taking phase of the packaging unit corresponding to the final taking period to be at least 100.

The invention also optionally proposes that the number of hormone daily units per taking phase of the packaging unit corresponding to the final taking period is at least 110.

The administration according to the invention can also be such that the number of hormone daily units per taking phase of the packaging unit corresponding to the final taking period is a maximum of 150.

It is also possible for the hormone daily units to in each case incorporate 0.5 to 3 mg inclusive of chlormadinone acetate, 1 to 3 mg inclusive of cyprotherone acetate, 0.05 to 0.2 mg inclusive of desogestrel, 1 to 3 mg inclusive of dienogest, 0.035 to 0.1 mg inclusive of gestoden, 0.025 to 0.5 mg inclusive of levonorgestrel, 0.25 to 3 mg inclusive of lynestrenol, 75 to 200 mg inclusive of medroxyprogesterone acetate, 0.175 to 1.5 mg inclusive of norethisterone, 0.1 to 0.3 mg inclusive or norgestimate, 0.015 to 0.75 mg inclusive of norgestrel, 0.25 to 3 mg inclusive of norethisterone acetate, 100 to

300 mg inclusive of norestisterone enanthate, 1.5 to 4 mg inclusive of drosperinone, 10 to 50 æg inclusive of ethinylestradiol, 25 to 50 æg inclusive of mestranol and/or 0.25 to 6 mg inclusive of estradiol (as a representative of natural estrogen).

In the administration form according to the invention it is also possible for at least one of the packaging units per taking pause to contain placebos in a number corresponding to the duration of the taking pause.

It is finally possible for the hormone component dosage to be successively reduced between taking periods.

The invention is based on the surprising finding that it is possible to solve the set problem in that the taking phases are successively extended between taking intervals. The number of vaginal spotting and breakthrough bleeding effects occurring at the start is reduced as compared with those regimens in which as from the start the taking phase is longer than 21 or 24 days. The regimens according to the invention are particularly suitable for first users of oral contraceptives wishing to reduce the number of withdrawal bleedings.

The administration of the dosage units takes place in such a way that said dosage units are bundled as a taking cycle. If administration is e.g. to be in tablet form, then the tablets for a taking cycle can be administered with a blister. The bundle or bundles required for a taking period are offered in pack form. The packs for different taking periods are clearly marked as such. As the number of taking cycles of the final taking period is a priori unknown, the number of bundles contained is based on reasons not predetermined by the process.

It is naturally possible to use other administration forms. Thus, in the case of oral administration capsules and the like can be used in place of tablets. Transdermal administration possibilities include plasters, creams, gels, etc. It is also possible to use

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CLAIMS

1. Process for hormonal contraception, in which in a plurality of substantially time-unlimited, linked taking periods and optionally having a sequence lasting several years and which in each case comprise at least one taking cycle with a duration-constant taking phase lasting several days within the particular taking period and a taking pause lasting several days, in which taking phase or phases per day administration takes place of a daily unit with at least one contraceptively acting hormone component, such as estrogen and/or gestagen, and in the taking pause or pauses administration takes place either of placebos free from any hormone component or the particular taking pause remains entirely administration-free and the duration of the taking phase or phases of at least the final taking period lasts at least 22 days, characterized in that the duration of the taking phase or phases in any taking period preceding a following taking period is shorter than in the in each case following taking period.

2. Process according to claim 1, characterized in that the final taking period starts at the latest with the tenth taking cycle.

3. Process according to claim 1 or 2, characterized in that in at least one taking period the particular taking phase precedes the particular taking pause.

4. Process according to claim 1 or 2, characterized in that in at least one taking period the particular taking pause precedes the particular taking phase.

5. Process according to one of the preceding claims, characterized in that the duration of at least one of the taking pauses is 4 to 10 days.

6. Process according to claim 5, characterized in that the duration of at least one of the taking pauses is 7 days.

7. Process according to one of the preceding claims, characterized in that the duration of the taking pauses in the final taking period is constant.

8. Process according to claim 7, characterized in that the duration of the taking pauses as from and including the first taking period is constant.

9. Process according to one of the preceding claims, characterized in that the duration of the taking phase or phases of at least the final taking period is at least 40 days.

10. Process according to claim 9, characterized in that the duration of the taking phase or phases of at least the final taking period is at least 45 days.

11. Process according to claim 9 or 10, characterized in that the duration of the taking phase or phases of at least the final taking period is at least 50 days.

12. Process according to one of the claims 9 to 11, characterized in that the duration of the taking phase or phases of at least the final taking period is at least 60 days.

13. Process according to one of the claims 9 to 12, characterized in that the duration of the taking phase or phases of at least the final taking period is at least 70 days.

14. Process according to one of the claims 9 to 13, characterized in that the duration of the taking phase or phases of at least the final taking period is at least 80 days.

15. Process according to one of the claims 9 to 14, characterized in that the duration of the taking phase or phases of at least the final taking period is at least 90 days.

16. Process according to one of the claims 9 to 15, characterized in that the duration of the taking phase or phases of at least the final taking period is at least 100 days.

17. Process according to one of the claims 9 to 16, characterized in that the duration of the taking phase or phases of at least the final taking period is at least 110 days.

18. Process according to one of the claims 9 to 17, characterized in that the duration of the taking phase or phases of at least the final taking period is a maximum of 150 days.

19. Process according to one of the preceding claims, characterized in that as hormone component or components use is made of chlormadinone acetate with a dosage per daily unit of 0.5 to 3 mg inclusive, cyproterone acetate 1 to 3 mg inclusive, desogestrel 0.05 to 0.2 mg inclusive, dienogest 1 to 3 mg inclusive, gestoden 0.035 to 0.1 mg inclusive, levonorgestrel 0.025 to 0.5 mg inclusive, lynestrenol 0.25 to 3 mg inclusive, medroxyprogesterone acetate 75 to 200 mg inclusive, norethisterone 0.175 to 1.5 mg inclusive, norgestimate 0.1 to 0.3 mg inclusive, norgestrel 0.015 to 0.75 mg inclusive, norethisterone acetate 0.25 to 3 mg inclusive, norestisterone enanthate 100 to 300 mg inclusive, drosperinone 1.5 to 4 mg inclusive, ethinylestradiol 10 to 50 æg inclusive, mestranol 25 to 50 æg inclusive and/or estradiol (as a representative of natural estrogen) 0.25 to 4 mg inclusive.

20. Process according to one of the preceding claims, characterized in that the hormone component dosage is successively decreased between taking periods.

21. Administration form for hormonal contraception, particularly for performing the process according to one of the preceding claims, with a plurality of packaging units, which in each case comprise at least one set of daily units to be administered within a taking cycle of a taking period, within which the duration of the taking phases is constant, comprising in each case a taking phase and a neighbouring taking pause and which in each case have a number of daily hormone units corresponding to the duration of the taking phase or phases, with in each case a content of at least one contraceptively acting hormone component, such as estrogen and/or gestagen, as well as optionally a number of placebos corresponding to the duration of the taking pause or pauses, the duration of the taking phase or phases of at least the last of the taking periods following

the first taking period is at least 22 days, characterized in that the number of daily hormone units in any packaging unit corresponding to a taking period preceding a following taking period is smaller than in the packaging unit corresponding to the in each case following taking period.

22. Administration form according to claim 21, characterized in that the last taking period commences at the latest with the tenth taking cycle.

23. Administration form according to claim 21 or 22, characterized in that in at least one taking period the taking phase precedes the taking pause.

24. Administration form according to claim 21 or 22, characterized in that in at least one taking period the taking pause precedes the taking phase.

25. Administration form according to one of the claims 21 to 24, characterized in that the number of daily hormone units per taking phase of the packaging unit corresponding to the last taking period is at least 40.

26. Administration form according to claim 25, characterized in that the number of daily hormone units per taking phase of the packaging unit corresponding to the last taking period is at least 45.

27. Administration form according to claim 25 or 26, characterized in that the number of daily hormone units per taking phase of the packaging unit corresponding to the last taking period is at least 50.

28. Administration form according to one of the claims 25 to 27, characterized in that the number of daily hormone units per taking phase of the packaging unit corresponding to the last taking period is at least 60.

29. Administration form according to one of the claims 25 to 28, characterized in that the number of daily hormone units per taking phase of the packaging unit corresponding to the last taking period is at least 70.

30. Administration form according to one of the claims 25 to 29, characterized in that the number of daily hormone units per taking phase of the packaging unit corresponding to the final taking period is at least 80.

31. Administration form according to one of the claims 25 to 30, characterized in that the number of daily hormone units per taking phase of the packaging unit corresponding to the last taking period is at least 90.

32. Administration form according to one of the claims 25 to 31, characterized in that the number of daily hormone units per taking phase of the packaging unit corresponding to the last taking period is at least 100.

33. Administration form according to one of the claims 25 to 32, characterized in that the number of daily hormone units per taking phase of the packaging unit corresponding to the last taking period is at least 110.

34. Administration form according to one of the claims 25 to 33, characterized in that the number of daily hormone units per taking phase of the packaging unit corresponding to the last taking period is a maximum of 150.

35. Administration form according to one of the claims 21 to 34, characterized in that the daily hormone units have in each case 0.5 to 3 mg inclusive of chlormadinone acetate, 1 to 3 mg inclusive of cyproterone acetate, 0.05 to 0.2 mg inclusive of desogestrel, 1 to 3 mg inclusive of dienogest, 0.035 to 0.1 mg inclusive of gestoden, 0.025 to 0.5 mg inclusive of levonorgestrel, 0.25 to 3 mg inclusive of lynestrenol, 75 to 200 mg inclusive of medroxyprogesterone acetate, 0.175 to 1.5 mg inclusive of norethisterone, 0.1 to 0.3 mg inclusive of norgestimate, 0.015 to 0.75 mg inclusive of

norgestrel, 0.25 to 3 mg inclusive of norethisterone acetate, 100 to 300 mg inclusive of norestisterone enanthate, 1.5 to 4 mg inclusive of drosperinone, 10 to 50 µg inclusive of ethinylestradiol, 25 to 50 µg inclusive of mestranol and/or 0.25 to 6 mg inclusive of estradiol (as a representative of natural estrogen).

36. Administration form according to one of the claims 21 to 34, characterized in that at least one of the packaging units per taking pause has placebos in a number corresponding to the duration of the particular taking pause.

37. Administration form according to one of the claims 21 to 36, characterized in that the hormone component dosage successively decreases between taking periods.

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(54) PHARMACEUTICAL COMPOSITION FOR USE AS A CONTRACEPTIVE

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(57) ABSTRACT

A pharmaceutical composition comprises, as a first active agent, 6β,7β;15β,16β-dimethylene-3-oxo-17α-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, 17α-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.

[0018] FIG. 4 is a graph showing the in vitro dissolution rate of ethinylestradiol from tablet cores, different lines representing different test batches; and

[0019] 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

[0020] Drospirenone, which may be prepared substantially as described in, e.g., U.S. Pat. No. 4,129,564 or WO 98/00738, 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.

[0021] 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 cm^2/g, and the following particle size distribution as determined under the microscope: not more than 2 particles in a given batch with a diameter of more than 30 μm, and preferably ≦20 particles with a diameter of ≧10 μm and ≦30 μm) in a pharmaceutical composition, rapid dissolution of the active compound from the composition occurs in vitro ("rapid dissolution" is defined as the dissolution of at least 70% over about 30 minutes, in particular at least 80% over about 20 minutes, of drospirenone from a tablet preparation containing 3 mg of drospirenone in 900 ml of water at 37° C. determined by the USP XXIII Paddle Method using a USP dissolution test apparatus 2 at 50 rpm). Instead of providing the drospirenone in micronized form, it is possible to dissolve it in a suitable solvent, e.g. methanol or ethyl acetate, and spray it onto the surface of inert carrier particles followed by incorporation of the particles containing drospirenone on their surface in the composition.

[0022] 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.

[0023] 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.

[0024] 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.

[0025] 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.

[0026] 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 properties and is therefore suitable for counteracting the water-retentive properties of ethinylestradiol.

[0027] In a particular embodiment, the invention relates to 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 each of said daily dosage units comprises a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg.

[0028] In one embodiment, the preparation further comprises 7 or less said daily dosage units containing no active agent. Alternatively, it is possible to include, in the dosage regimen, a period of 7 days or less during which no dosage units are ingested. For compliance reasons, however, it may be preferred to include an appropriate number of blanks in the preparation, in which case the total number of daily dosage units in the preparation is at least 28. The inclusion of blanks, or the pill-free days, will then trigger withdrawal bleeding.

[0029] The preparation may be a one-phase composition, i.e. a preparation wherein the amounts of either active agent remains constant for the entire at least 21-day period, or the amounts of either or both active agents may be varied over the at least 21-day period to generate a multiple-phase preparation, e.g. a two- or three-phase preparation, substantially as disclosed in, e.g., EP 148 724. In case of multiple-phase preparation, it may be possible to include a natural estrogen such as estradiol, e.g. in an amount of from about 0.5 mg to about 4 mg per day, instead of ethinylestradiol.

unit dosage form, or sprayed from a solution onto particles of an inert carrier in admixture with one or more pharmaceutically acceptable excipients that promote dissolution of the drospirenone and ethinylestradiol so as to promote rapid dissolution of drospirenone and preferably ethinylestradiol on oral administration. Examples of suitable excipients include fillers, e.g. sugars such as lactose, glucose or sucrose, sugar alcohols such as mannitol, sorbitol or xylitol, starch such as wheat, corn or potato starch, modified starch or sodium starch glycolate, lubricants such as talc, 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.

[0043] Tablets may conveniently be coated with a suitable film-forming agent, e.g. hydroxypropylmethyl cellulose, hydroxypropyl cellulose or ethyl cellulose, to which a suitable excipient may optionally be added, e.g. a softener such as glycerol, propylene glycol, diethylphthalate or glycerol triacetate, filler such as sucrose, sorbitol, xylitol, glucose or lactose, a colorant such as titanium hydroxide, etc.

[0044] The present composition may also be formulated in liquid form, e.g. as a solution, suspension or emulsion, together with conventional diluents or excipients in a manner known per se in the pharmaceutical art.

[0045] A packaging unit comprising the daily dosage units described above may be prepared in a manner analogous to that of making other oral contraceptives. This may for instance be a conventional blister pack or any other form known for this purpose, for instance a pack comprising the appropriate number of dosage units (in this case at least 21, or for particular applications, 28 or a multiple of 28) in a sealed blister pack with a cardboard, paperboard, foil or plastic backing and enclosed in a suitable cover. Each blister container may conveniently be numbered or otherwise marked, e.g. starting with the first of the at least 21 dosage units that contain the combination of drospirenone and ethinylestradiol, optionally followed by 7 or less empty blisters or by the 7 or less dosage units that contain no active agent or that only contain ethinylestradiol (although the numbering may also start with the first of the 7 or less dosage units that only contain ethinylestradiol).

[0046] It is also envisaged that the present composition may be in the form of a parenteral formulation such as a subcutaneous implant or transdermal formulation. For making implants, the active agents may suitably be formulated together with one or more polymers that are gradually eroded or degraded when in use, e.g. silicone polymers, ethylene vinylacetate, polyethylene or polypropylene.

[0047] Where transdermal formulations are concerned, they may be prepared in the form of matrices or membranes or as fluid or viscous formulations in oil or hydrogels. For transdermal patches, an adhesive which is compatible with the skin should be included, such as polyacrylate, a silicone adhesive or polyisobutylene, as well as a foil made of, e.g. polyethylene, polypropylene, ethylene vinylacetate, polyvinylchloride, polyvinylidene chloride or polyester, and a removable protective foil made from, e.g., polyester or paper coated with silicone or a fluoropolymer. For the preparation of transdermal solutions or gels, water or organic solvents or mixtures thereof may be used. Transdermal gels may furthermore contain one or more suitable gelling agents or thickeners such as silicone, tragacanth, starch or starch derivatives, cellulose or cellulose derivatives or polyacrylic acids or derivatives thereof. Transdermal formulations may also suitably contain one or more substances that enhance absorption though the skin, such as bile salts or derivatives thereof and/or phospholipids. Suitable transdermal formulations may, for instance, be made in a manner analogous to that described in WO 94/04157 for 3-ketodesogestrel. Alternatively, transdermal formulations may be prepared according to a method disclosed in, e.g., B W Barry, "Dermatological Formulations, Percutaneous Absorption", Marcel Dekker Inc., New York-Basel, 1983, or Y W Chien, "Transdermal Controlled Systemic Medications", Marcel Dekker Inc., New York-Basel, 1987.

[0048] The present invention is further described in the following examples which are not in any way intended to limit the scope of the invention as claimed.

EXPERIMENTAL

Example 1

[0049] Preparation of Tablets Containing Drospirenone and Ethinylestradiol

Tablet cores of the following composition	
micronized drospirenone	3.00 mg
micronized ethinylestradiol	0.03 mg
lactose monohydrate	48.17 mg
corn starch	14.40 mg
modified starch	9.60 mg
polyvinylpyrrolidone 25,000	4.00 mg
magnesium stearate	0.80 mg

[0050] were prepared by charging a fluidized bed granulator with 31.68 kg corn starch, 21.12 kg modified starch, 6.60 micronized drospirenone, 0.066 kg micronized ethinylestradiol and 105.974 kg lactose monohydrate and activating the fluidized bed. An aqueous solution of 8.80 kg polyvinylpyrrolidone 25,000 in 46.20 kg purified water was sprayed continuously onto the fluidized bed while drying by heating the air stream of the fluidized bed. At the end of the process 1.76 kg magnesium stearate was sucked into the granulator and mixed with the granules by maintaining the fluidized bed. The resulting granulate was pressed into tablet cores by compression using a rotary tablet press.

[0051] 2.22464 kg of hydroxypropylmethylcellulose and 0.44528 macrogol 6000 were dissolved in 14.67 kg purified water. 0.44528 kg talc, 1.22430 kg titanium dioxide and 0.00050 kg ferric oxide pigment were suspended in 10.26 kg purified water with stirring and homogenized. The solution and suspension were combined and used to coat the tablet cores by continuous application of the coating suspension in a coater.

Example 2

[0052] Dissolution of Drospirenone From Tablets

[0053] The rate of dissolution of drospirenone from the tablets prepared in Example 1 was determined by the USP

[0072] The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

[0073] Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The preceding preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

[0074] The entire disclosure of all applications, patents and publications, cited above and below, and of corresponding U.S. application Ser. No. 09/386,274, are hereby incorporated by reference.

[0075] From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

1. A pharmaceutical composition comprising, as a first active agent, 6β,7β;15β,16β-dimethylene-3-oxo-17α-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, 17α-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.

2. A composition according to claim 1 wherein the drospirenone is in micronized form or sprayed from a solution onto particles of an inert carrier.

3. A composition according to claim 1 or 2, comprising drospirenone in an amount corresponding to a daily dosage of from about 2.5 mg to about 3.5 mg, in particular about 3 mg.

4. A composition according to claim 1 wherein the ethinylestradiol is in micronized form or sprayed from a solution onto particles of an inert carrier.

5. A composition according to claim 1, comprising ethinylestradiol in an amount corresponding to a daily dosage of from about 0.015 mg to about 0.04 mg, in particular from about 0.02 mg to about 0.03 mg.

6. A composition according to claim 1, comprising 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, in particular comprising an amount of drospirenone corresponding to a daily dosage of about 3.0 mg and ethinylestradiol in an amount corresponding to a daily dosage of 0.03 mg.

7. A composition according to claim 1 wherein the pharmaceutically acceptable carrier or excipient is selected so as to promote rapid dissolution of the first and second active agents.

8. A composition according to claim 1 wherein at least 70% of the first and second active substances are released within 30 minutes of administration thereof.

9. A composition according to claim 8, wherein at least 80% of the first and second active agents are released within 20 minutes of administration thereof.

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

11. A preparation according to claim 10, which additionally comprises 7 or less daily dosage units containing no active agent intended for oral administration subsequent to the period of at least 21 consecutive days, the total number of daily dosage units being at least 28.

12. A preparation according to claim 10 or 11, wherein the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol is 21, 22, 23 or 24, and wherein the number of daily dosage units containing no active agent is 7, 6, 5 or 4.

13. A preparation according to claim 10, wherein the number of daily dosage units comprising the combination of drospirenone and ethinylestradiol is 28, or a multiple of 28 such as 2-4, in particular 2 or 3, times 28.

14. A preparation according to claim 13, which additionally comprises a number of daily dosage units comprising the combination of drospirenone and ethinylestradiol of 21, 22, 23 or 24, and a number of daily dosage units containing no active agent of 7, 6, 5 or 4.

15. A preparation according to claim 10, wherein the at least 21 daily dosage units comprise drospirenone and ethinylestradiol in micronized form or sprayed from a solution onto particles of an inert carrier.

16. A preparation according to claim 10 wherein the at least 21 daily dosage units comprise drospirenone in an amount of from about 2.5 mg to about 3.5 mg, in particular about 3 mg, and ethinylestradiol in an amount of from about 0.015 mg to about 0.04 mg, in particular from about 0.015 mg to about 0.03 mg.

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

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

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

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

21. A preparation according to claim 18, wherein the at least 21 daily dosage units comprise drospirenone in an amount of from about 2.5 mg to about 3.5 mg, in particular

about 3 mg, and ethinylestradiol in an amount of from about 0.015 mg to about 0.04 mg, in particular from about 0.02 mg to about 0.03 mg.

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

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

24. A method according to claim 23, wherein the amount of drospirenone is in the range of from about 2.5 mg to about 3.5 mg, in particular about 3 mg of drospirenone per day.

25. A method according to claim 23, wherein the amount of ethinylestradiol is from about 0.015 mg to about 0.04 mg, in particular from about 0.015 to about 0.03 mg per day.

26. A method of preventing or treating androgen-induced disorders in a female mammal, in particular a female human, comprising administering, to said mammal, an amount of drospirenone in the range of from about 2 mg to about 4 mg per day, together with an amount of ethinylestradiol of from about 0.01 mg to about 0.05 mg per day, said amounts being effective to prevent or treat androgen-induced disorders in said mammal.

27. A method according to claim 26, wherein the androgen-induced disorder is acne.

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

29. A method according to claim 28, wherein the daily dosage units comprising the combination of drospirenone and ethinylestradiol are administered for 21, 22, 23 or 24 consecutive days, and wherein no daily dosage units or daily dosage units containing no active agent are administered for 7, 6, 5 or 4 consecutive days.

30. A method according to claim 28, wherein the daily dosage units comprising the combination of drospirenone and ethinylestradiol are administered for 28 consecutive days.

31. A method according to claim 28, wherein the daily dosage units comprising the combination of drospirenone and ethinylestradiol are administered for 2-4, preferably 2 or 3, times 28 consecutive days, followed by administration of the daily dosage units comprising the combination of drospirenone and ethinylestradiol for 21 consecutive days and subsequently administration of the daily dosage units containing no active agent, or alternatively no daily dosage units, for 7 consecutive days.

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

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

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

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

* * * * *

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(12) **United States Patent**
Gast

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(54) **ORAL CONTRACEPTIVE**

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(52) **U.S. Cl.** **514/170**; 514/843

(58) **Field of Search** 514/170, 843

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

Lachnit-Fixson (U.S. Pat. No. 4,621,079) discloses triphasic 21-day progestin/estrogen combination regimens in which a combination of 40–70 μg GTD and 20–35 μg EE is administered for 4–6 days in the first phase; 50–100 μg GTD and 30–50 μg EE is administered for 4–6 days in the second phase; and 80–120 μg GTD and 20–50 μg EE is administered for 9–11 days in the third phase. Placebo is administered for 7 days following the 21-day contraceptive steroid regimen.

Pasquale (U.S. Pat. No. 4,530,839) discloses triphasic 21-day progestin/estrogen combination regimens in which a dose of 20–50 μg EE is administered in all three phases in combination with a contraceptively effective daily dose of progestin in the first phase, 1.5–2 times that dose of progestin in the second phase, and 2–2.5 times the first phase dose of progestin in the third phase. Each of the three phases is 7 days long. A specific regimen discloses 20–50 μg EE in combination with 500 μg LNg, 750 μg LNg, and 1 mg LNg during each of the three 7-day phases, respectively.

Edgren (U.S. Pat. No. 4,390,531) discloses triphasic 21-day progestin/estrogen combination regimens in which a dose of 20–40 μg EE (or another estrogen in an equivalent dosage) is administered in all three phases in combination with 0.3–0.8 mg NE (or another progestin in an equivalent dosage) for 5–8 days in the first phase, twice the dose of NE for 7–11 days in the second phase, and the dose of NE being the same as in the first phase for 3–7 days in the third phase. It is preferred that each of the three phases is 7 days. Placebo is administered for 6–8 days following administration of the contraceptive steroid combination. A specific regimen discloses a first phase of 7 days of 0.5 mg NE in combination with 35 μg EE, a second 7 day phase of 1.0 mg NE in combination with 35 μg EE, and a third 7 day phase of 0.5 mg NE in combination with 35 μg EE.

Moore (DE 4313926 A1) discloses bridged triphasic regimens consisting of the administration of a combination of 10–50 μg LNg and 5–20 μg EE from days 1–7 of the menstrual cycle; of 50–75 μg LNg and 5–20 μg EE from days 8–14 of the menstrual cycle; of 75–125 μg LNg and 5–30 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. 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 μg EE followed by 18 days of the combination of 150 μg LNg and 20 μg EE. Regimen (c) in Erlich provides a total steroidal load of 2.7 mg of LNg and 560 μg EE per 28 day cycle.

DESCRIPTION OF THE INVENTION

This invention provides a monophasic combination progestin/estrogen oral contraceptive regimen for females of child-bearing age that provides effective contraception, good cycle control, and minimal side effects while greatly reducing the total contraceptive steroid administered (particularly the estrogenic component) per 28-day cycle. To achieve the substantial reduction in the total contraceptive steroid administered per cycle while maintaining good cycle control, the low dose progestin/estrogen combination is administered for 23–25 days per cycle. Administration of the contraceptive progestin/estrogen combination is begun on the first day of menses (day 1), and continued for 23–25 consecutive days. Following the 23–25-day administration period, a non-contraceptive placebo (devoid of progestins and estrogens) can be provided for 3–5 days to aid in compliance with the desired 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 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-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; 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, it is preferred that the daily dosage of ethinyl estradiol is 10–20 μg, with 15 μg 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 μg ethinyl estradiol.

Following the 23–25-day period, a non-contraceptive placebo, which may contain an iron supplement, such as 75 mg of ferrous fumerate, 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 μg	15 μg
B	125 μg	15 μg
C	75 μg	15 μg

-continued

PREFERRED DAILY DOSAGES

Regimen	Trimegestone	Ethinyl Estradiol
D	50 μg	15 μg
E	40 μg	15 μg

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

PREFERRED DAILY DOSAGES

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

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

PREFERRED DAILY DOSAGES

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

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 μg
Ethinyl estradiol, 15 μg
Microcrystaline 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 μg trimegestone, 250 μg–4 mg dienogest, or 250 μg–4 mg mg drospirenone, and an estrogen at a daily dosage equivalent in estrogenic activity to 10–20 μg 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 fumerate. 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 μg trimegestone, and 250 μg–4 mg dienogest, and an estrogen at a daily dosage equivalent in estrogenic activity to 10–20 μg ethinyl estradiol for 23–25 days beginning on day 1 of the menstrual cycle, and wherein the same dosage of the progestin and estrogen combination is administered in each of the 23–25 days.

2. The method according to claim 1, wherein the estrogen is selected from the group consisting of ethinyl estradiol; 17β-estradiol; conjugated estrogens, USP; estrone or a salt thereof; and mestranol.

3. The method according to claim 2, wherein the estrogen is ethinyl estradiol.

4. The method according to claim 3, wherein the progestin/estrogen combination is administered for 24 days per menstrual cycle beginning on day 1 of the menstrual cycle.

5. The method according to claim 4 wherein the daily dosage of ethinyl estradiol is 15 μg.

6. The method according to claim 5, wherein the progestin is trimegestone.

7. The method according to claim 6, wherein the daily dosage of trimegestone is 250 μg.

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

9. The method according to claim 6, wherein the daily dosage of trimegestone is 75 μg.

10. The method according to claim 6, wherein the daily dosage of trimegestone is 50 μg.

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

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 μg.

16. The method according to claim 11, wherein the daily dosage of dienogest is 750 μg.

17. The method according to claim 11, wherein the daily dosage of dienogest is 500 μg.

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.

20. A contraceptive kit adapted for oral administration consisting of 23–25 separate dosage units, said dosage units each containing a combination of a progestin at a dosage selected from the group consisting of 40–500 μg trimegestone, and 250 μg–4 mg dienogest, and an estrogen at a dosage equivalent to estrogenic activity to 10–30 μg ethinyl estradiol, wherein each of the dosage units contains the same dosage of progestin and estrogen.

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

22. The contraceptive kit according to claim 21, wherein the estrogen is ethinyl estradiol.

23. The contraceptive kit according to claim 22 in which the number of dosage units is 24.

24. A contraceptive kit adapted for oral administration which comprises 28 dosage separate units, 23–25 of said dosage units each containing a combination of a progestin at a dosage selected from the group consisting of 40–500 μg trimegestone, and 250 μg–4 mg dienogest, and an estrogen at a dosage equivalent in estrogenic activity to 10–30 μg ethinyl estradiol, wherein each of the dosage units contains the same dosage of progestin and estrogen; and 3–5 of said dosage units each containing a non-contraceptive placebo, wherein each of the 23–25 dosage units contains the same dosage of progestin and estrogen.

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

(57) Abstract

This invention provides a method of contraception which comprises administering to a female of child bearing age for a combination of a progestin at a daily dosage of 40-500 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, and wherein the same dosage of the progestin and estrogen combination is administered in each of the 23-25 days.

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

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

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

DESCRIPTION OF THE INVENTION

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

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 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-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; 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, it is preferred that the daily dosage of ethinyl estradiol is 10-20 µg, with 15 µg 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 µg ethinyl estradiol.

Following the 23-25-day period, a non-contraceptive placebo, which may contain an iron supplement, such as 75 mg of ferrous fumerate, 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 µg	15 µg
B	125 µg	15 µg
C	75 µg	15 µg
D	50 µg	15 µg
E	40 µg	15 µg

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

PREFERRED DAILY DOSAGES

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

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

PREFERRED DAILY DOSAGES

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

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 µg
Ethinyl estradiol, 15 µg
Microcrystaline 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 µg trimegestone, 250 µg - 4 mg dienogest, or 250 µg - 4 mg mg drospirenone, and an estrogen at a daily dosage equivalent in estrogenic activity to 10-20 µg 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 fumerate. 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 µg trimegestone, 250 µg - 4 mg dienogest, and 250 µg - 4 mg drospirenone, and an estrogen at a daily dosage equivalent in estrogenic activity to 10-20 µg ethinyl estradiol for 23-25 days beginning on day 1 of the menstrual cycle, and wherein the same dosage of the progestin and estrogen combination is administered in each of the 23-25 days.

2. The method according to claim 1, wherein the estrogen is selected from the group consisting of ethinyl estradiol; 17β-estradiol; conjugated estrogens, USP; estrone or a salt thereof; and mestranol.

3. The method according to claim 2, wherein the estrogen is ethinyl estradiol.

4. The method according to claim 3, wherein the progestin/estrogen combination is administered for 24 days per menstrual cycle beginning on day 1 of the menstrual cycle.

5. The method according to claim 4 wherein the daily dosage of ethinyl estradiol is 15 µg.

6. The method according to claim 5, wherein the progestin is trimegestone.

7. The method according to claim 6, wherein the daily dosage of trimegestone is 250 µg.

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

9. The method according to claim 6, wherein the daily dosage of trimegestone is 75 µg.

10. The method according to claim 6, wherein the daily dosage of trimegestone is 50 µg.

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

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 µg.

16. The method according to claim 11, wherein the daily dosage of dienogest is 750 µg.

17. The method according to claim 11, wherein the daily dosage of dienogest is 500 µg.

18. The method according to claim 5, wherein the progestin is drospirenone.

19. The method according to claim 18, wherein the daily dosage of drospirenone is 3 mg.

20. The method according to claim 18, wherein the daily dosage of drospirenone is 2 mg.

21. The method according to claim 18, wherein the daily dosage of drospirenone is 1 mg.

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

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

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

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

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

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

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

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

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1: Eur J Contracept Reprod Health Care. 2003 Sep;8(3):162-9.

Use of an oral contraceptive containing drospirenone in an extended regimen.

Sillem M, Schneidereit R, Heithecker R, Mueck AO.

Gynecological Clinic, Aschaffenburg, Germany.

As well as providing reliable contraception, modern low-dose oral contraceptives may offer some non-contraceptive advantages. Positive effects on problems such as edema with weight increase and breast tenderness, bloating, dysmenorrhea, and an improvement in skin and hair condition have been reported in several studies using an oral contraceptive containing drospirenone. If these disorders are cycle-dependent, use of the contraceptive in an extended regimen may be of additional benefit. The study reported in this paper followed 1433 women, 175 of whom took the drospirenone-containing pill continuously for between 42 and 126 days. Some symptoms of the premenstrual syndrome were influenced very satisfactorily by administration in an extended regimen.

PMID: 14667028 [PubMed - indexed for MEDLINE]

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1: Contraception. 2004 Jan;69(1):37-42.

Related Articles, Links

Attitude of German women and gynecologists towards long-cycle treatment with oral contraceptives.

Wiegratz I, Hommel HH, Zimmermann T, Kuhl H.

Center of Obstetrics and Gynecology, University Hospital of Frankfurt, am Main, Frankfurt, Germany.

Long-cycle regimens with continuous use of oral contraceptives (OCs) for 3 or 6 months followed by a hormone-free interval of 7 days may reduce or prevent cycle-dependent and menses-related complaints. A representative survey carried out with 1195 German women in different age groups revealed that only 26-35% of the women aged between 15 and 49 years preferred monthly bleeding, while 37-46% wished to never bleed. The reasons for the refusal of regular menstruations were fewer severe menstrual complaints, better hygiene, higher quality of life, and less blood loss. Among the women who preferred regular withdrawal bleeding during the use of OCs, the main reasons were fear of pregnancy, infertility and adverse effects, and that menstruations were natural. Between 32% and 54% of the women would suppress menstruation sporadically and 11-14% for a longer period of time. After continuous treatment with a combination of 30 microg ethinyl estradiol and 2 mg dienogest for 6 months, the majority of women preferred the long-cycle regimen as compared to the conventional OC regimen despite a higher rate of irregular bleeding. Bleeding occurred primarily in first-time users of OC, particularly during the administration of the second OC pack. A survey carried out with German gynecologists revealed that most physicians prescribed extended OC cycles primarily for medical reasons, e.g., dysmenorrhea, hypermenorrhea, endometriosis and premenstrual dysphoric disorder. The gynecologists preferred a regimen with three packs of extended use of OCs.

PMID: 14720618 [PubMed - indexed for MEDLINE]

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Long-cycle treatment of oral contraceptives.
Wiegratz I, Kuhl H.
Gynakologische Praxis. 2003; 27(3):

Postponement or withdrawal bleeding: an option for every woman using combined oral contraceptives?
Kuhl H.
Expert Opinion on Pharmacotherapy. 2005 Jan; 6(1):

Cycle control and side effects of a new oral contraceptive containing estradiol valerate and dienogest in a monophasic regimen.
Kuhl H, Schubert G.
Contraception. 2004 Jan; 69(1):

Postponing menstruation and the experience of menstrual bleeding in relation to menstrual cycle control, oral contraceptive use, and hormone replacement therapy.
Kuhl H.
Climacteric. 2004 Dec; 7(4):

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-49-

240 240

Atrás

La página o páginas que se imprimirán.

Registro: 1

Título: An open-label, multicenter, noncomparative safety and efficacy study of Mircette, a low-dose estrogen-progestin oral contraceptive. The Mircette Study Group.

Fuente: American Journal Of Obstetrics And Gynecology [Am J Obstet Gynecol] 1998 Jul; Vol. 179 (1), pp. S2-8.

Tipo de publicación: Clinical Trial; Journal Article; Multicenter Study

Idioma: English

Journal Information: *Country of Publication:* UNITED STATES *NLM ID:* 0370476 *Publication Model:* Print *Cited Medium:* Print *ISSN:* 0002-9378 (Print) *NLM ISO Abbreviation:* Am. J. Obstet. Gynecol. *Subsets:* Core Clinical (AIM); MEDLINE

Términos MeSH: Contraceptives, Oral, Combined/*therapeutic use
Desogestrel/*therapeutic use
Ethinyl Estradiol/*therapeutic use
Menstruation/*drug effects
Adolescent; Adult; Contraceptives, Oral, Combined/adverse effects; Desogestrel/administration & dosage; Desogestrel/adverse effects; Dose-Response Relationship, Drug; Ethinyl Estradiol/administration & dosage; Ethinyl Estradiol/adverse effects; Female; Humans; Middle Aged

Resumen: OBJECTIVE: The primary efficacy and safety of Mircette (brand of desogestrel/ethinyl estradiol and ethinyl estradiol), an oral contraceptive containing 150 microg desogestrel and 20 microg ethinyl estradiol given for 21 days, followed by 2 days of placebo and then 5 days 10 microg ethinyl estradiol, was evaluated. STUDY DESIGN: In a large, open-label, 18-month, multicenter trial, a total of 1143 of 1250 healthy female subjects contributed to the determination of extent of exposure, for an equivalent of 1080.8 woman-years of use. RESULTS: Absence of withdrawal bleeding occurred in 5.5% of total cycles and intermenstrual bleeding occurred in 12.0% of total cycles. Breakthrough spotting was more common than breakthrough bleeding. The Pearl Index for total pregnancies during treatment was 1.02/100 woman-years. Fewer than 3% of subjects discontinued study participation, primarily because of menstrual problems, indicating that Mircette was an oral contraceptive acceptable to the women studied. Overall 73.6% of all subjects reported one or more adverse events, and a total of 43.9% of subjects reported drug-related adverse events. The most common drug-related adverse events reported included headache (8.5%), breast pain (7.3%), dysmenorrhea (4.2%), and menstrual disorder (4.2%). There were no reports of venous thromboembolic events or of significant changes in blood pressure, lipid metabolism, or serum glucose level. CONCLUSION: The study confirmed that Mircette is a safe and efficacious oral contraceptive that is well tolerated and acceptable to women who have previously used oral contraceptives, as well as first-time users.

CAS Registry Number: 0 (Contraceptives, Oral, Combined)
54024-22-5 (Desogestrel)
57-63-6 (Ethinyl Estradiol)
71138-35-7 (Oviol)

Fecha(s) de la *Date Created:* 19980903 *Date Completed:* 19980903 *Latest Revision:*

10
244
241

entrada:	20041117
Código de actualización:	20071207
PMID:	9704812
Base de datos:	MEDLINE

Atrás

242

Atrás

2 página o páginas que se imprimirán:

Registro: 1

Título: Selectivity and minimal androgenicity of norgestimate in monophasic and triphasic oral contraceptives.

Autor(es): Anderson FD

Author's Address: Eastern Virginia Medical School, Norfolk.

Fuente: Acta Obstetricia Et Gynecologica Scandinavica. Supplement [Acta Obstet Gynecol Scand Suppl] 1992; Vol. 156, pp. 15-21.

Tipo de publicación: Journal Article; Meta-Analysis

Idioma: English

Journal Information: *Country of Publication:* DENMARK *NLM ID:* 0337655 *Publication Model:* Print *Cited Medium:* Print *ISSN:* 0300-8835 (Print) *Subsets:* MEDLINE

Términos MeSH: Contraceptives, Oral, Combined/*pharmacology
Norgestrel/*analogs & derivatives
Acne Vulgaris/chemically induced; Animals; Body Weight/drug effects; Carbohydrates/blood; Contraceptives, Oral, Combined/administration & dosage; Ethinyl Estradiol/administration & dosage; Ethinyl Estradiol/pharmacology; Female; Humans; Lipids/blood; Meta-Analysis as Topic; Norgestrel/administration & dosage; Norgestrel/pharmacology; Prolactin/blood; Receptors, Androgen/drug effects; Receptors, Progesterone/drug effects; Sex Hormone-Binding Globulin/metabolism

Resumen: The contraceptive progestin norgestimate (NGM) has a high affinity for uterine progestin receptors and a lack of affinity for androgen receptors similar to that of natural progesterone. NGM's selectivity results in excellent efficacy, cycle control, and minimal androgenicity when it is combined with ethinyl estradiol (EE). Clinical studies of a monophasic regimen of NGM/EE indicate a positive impact on lipid metabolism, revealing an increase in serum levels of high-density lipoprotein cholesterol with a concomitant and significant decrease in the low-density lipoprotein/high-density lipoprotein cholesterol ratio. Little impact on carbohydrate metabolism was noted. Serum levels of sex hormone binding globulin, an indicator of androgen-estrogen balance, also increased significantly with NGM/EE in accordance with its low androgenic activity. A significant between-regimen difference in SHBG was seen in a comparison study of NGM/EE and LNG/EE triphasic formulations (a mean rise of 68.6% with NGM/EE vs a decrease of 6.1% with LNG/EE). NGM's lack of estrogenicity was evidenced by unchanged prolactin levels and absence of effect on the coagulation system. In a large study of the monophasic formulation in 59,701 women, some improvement in acne was reported as well as minimal weight gain. An overview of clinical data is provided from United States and European trials as well as some preclinical data relevant to NGM's selectivity.

Índice aportado: *Indexing Agency:* PIP *Local ID #:* 076695. *Indexing Agency:* POP *Local ID #:* 00217116.
Keywords: Acne*; Biology; Body Weight--changes*; Carbohydrate Metabolic Effects*; Contraception; Contraceptive Agents; Contraceptive Agents, Female; Contraceptive Agents, Progestin; Contraceptive Effectiveness*; Contraceptive Methods--beneficial

effects; Contraceptive Methods--side effects; Dermatitis; Diseases; Family Planning; Hormone Receptors*; Lipid Metabolic Effects*; Lipids; Membrane Proteins; Metabolic Effects; Norgestimate*; Oral Contraceptives, Combined--beneficial effects; Oral Contraceptives, Combined--side effects; Oral Contraceptives, Phasic--beneficial effects*; Oral Contraceptives, Phasic--side effects*; Oral Contraceptives--beneficial effects; Oral Contraceptives--side effects; Physiology

Note: TJ: ACTA OBSTETRICIA ET GYNECOLOGICA SCANDINAVICA. SUPPLEMENT.

Local Abstract: [PIP] The contraceptive progestin norgestimate (NGM) has a high affinity for uterine progestin receptors and a lack of affinity for androgen receptors, similar to that of natural progesterone. NGM's selectivity results in excellent efficacy, cycle control, and minimal androgenicity when it is combined with ethinyl estradiol (EE). Clinical studies of a monophasic regimen of NGM/EE indicate a positive impact on lipid metabolism, revealing an increase in serum levels of high-density lipoprotein (HDL)-cholesterol with a concomitant and significant decrease in the low-density lipoprotein/HDL cholesterol ratio. Little impact on carbohydrate metabolism was noted. Serum levels of sex hormone binding globulin (SHBG), an indicator of androgen-estrogen balance, also increased significantly with NGM/EE in accordance with its low androgenic activity. A significant between-regimen difference in SHBG was seen in a comparison study of NGM/EE and levonorgestrel (LNG)/EE triphasic formulations (a mean increase of 68.6% with NGM/EE vs. a decrease of 6.1% with LNG/EE). NGM's lack of estrogenicity was seen through unchanged prolactin levels and an absence of effect on the coagulation system. In a large study of the monophasic formulation in 59,701 women, some improvements in acne were reported as well as in minimal weight gain. An overview of clinical data is provided from the US and European trials as well as some preclinical data relevant to NGM's selectivity.

CAS Registry Number: 0 (Carbohydrates)
0 (Contraceptives, Oral, Combined)
0 (Lipids)
0 (Receptors, Androgen)
0 (Receptors, Progesterone)
0 (Sex Hormone-Binding Globulin)
35189-28-7 (norgestimate)
57-63-6 (Ethinyl Estradiol)
6533-00-2 (Norgestrel)
9002-62-4 (Prolactin)

Fecha(s) de la entrada: *Date Created:* 19920924 *Date Completed:* 19920924 *Latest Revision:* 20071115

Código de actualización: 20071207

PMID: 1324552

Base de datos: MEDLINE

Atrás

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AA 8567146

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244
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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:----------

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27 FEB 2008

FERNANDO CARRERA
NOTARIO NOVENO
BOGOTA, D.C.

PRIMERO: Que obra en su carácter 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

ESTE PAPEL NO TIENE COSTO ALGUNO PARA EL USUARIO

DERECHOS NOTARIALES: $ 49.600.oo

RESOLUCION No. 4188 del 28 de Diciembre del 2001

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 :

JOSE LUIS REYES VILLAMIZAR

C.C. No. 79.152.473

TEL: 621-2631

DIANA BEATRIZ LOPEZ

DIANA BEATRIZ LOPEZ

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Santafé de Bogotá, D.C. 05 JUL. 2002

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BOGOTA, D.C.

REPUBLICA DE COLOMBIA
GLENA ARBIAGA SALAS
33
Notaria Encargada
BOGOTA, D.C.

01

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246

CAMARA DE COMERCIO DE BOGOTA

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080227 Hora Certificado 10:19:58

Operacion : 02NA40227026 PAGINA No. 1

****

EN JUNIO DE ESTE A?O SE ELEGIR? JUNTA DIRECTIVA Y REVISOR FISCAL DE LA CAMARA DE COMERCIO. LAS INSCRIPCIONES DE CANDIDATOS DEBEN HACERSE EN LA PRIMERA QUINCENA DE MAYO. PARA INFORMACION DETALLADA DIRIGIRSE A LA SEDE PRINCIPAL O COMUNICARSE AL TELEFONO 8861339.

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	FECHA DOC	ORIGEN	FECHA INS	NRO INS	LIBRO
E.P. 1104	30/06/1959	NOTARIA CUARTA DE CALI	07/07/1959		
E.P. 2309	26/12/1959	NOTARIA CUARTA DE CALI	22/12/1959		
E.P. 1725	24/07/1962	NOTARIA CUARTA DE CALI	26/07/1962		
E.P. 1824	31/07/1963	NOTARIA CUARTA DE CALI	14/08/1963		

*** CONTINUA ***

CERTIFICADO DE CALIDAD No. 8271 19467 20089 24528 26360 NTC-ISO 9001:2000

PREMIO COLOMBIANO A LA CALIDAD DE LA GESTION

IMPRESO POR DATAPREMIUM S.A. NIT. 830.076.171-5 6/50 09-2007

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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Operacion : 02NA402227026 PAGINA No: 4

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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) EJECUTAR Y HACER CUMPLIR LOS ACUERDOS Y 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

*** CONTINUA ***

01

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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****

SEGUNDO SUPLENTE DEL GERENTE

ROBERTO MARA VENTURA CRISPINO

C.C.9086003

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

*** CONTINUA ***

ICONTEC CERTIFICADO DE GESTION Certificado No. 027-1 NTC-ISO 9001:2000

PREMIO COLOMBIANO A LA CALIDAD DE LA GESTIÓN

IMPRESO POR SERVIGRAFICOS S.A. NIT 830.053.717-5 2007-09-2007

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080227 Hora Certificado 10:19:58

Operacion 02NA10227026 PAGINA No. 6

****

PRIMER RENGLON

ESTHER ISABEL VENTURA DE RENDON

C.C.38979831

SEGUNDO RENGLON

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. 14075 DEL LIBRO IX

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

*** CONTINUA ***

01

CAMARA DE COMERCIO DE BOGOTA

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080227 Hora Certificado : 10:19:58

Operación : 02NA40227026 PAGINA No.: 7

****

FUE(RON) NOMBRADO(S):

REVISOR FISCAL PRINCIPAL
ALFREDO LOPEZ CAMPO
C.C. 8241912

REVISOR FISCAL SUPLENTE
GEOVANA GONZALEZ CALINDO
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 AÑO 2000

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 AÑO 2007

***** CONTINUA *****

PREMIO COLOMBIANO A LA CALIDAD DE LA GESTIÓN

IMPRESO POR BARRANQUILLA S.A. NIT. 890103711-8 05/03/2007

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080227 Hora Certificado 10:19:58

Operacion : 02NA402270026 PAGINA No: 3

****

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO 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 A?O 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 27 DIAS DEL MES DE FEBRERO DEL A?O 2008 HORA: 10:17:20

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

V9
250

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-120228- -00006-0000

Fecha: 2008-02-27 16:19:28 Dep: 2020 NULIDAD RELACIONE
Tra: 11 PATENTE LEY Eve: 379 PASE NACIONAL II
Act: 400 OPOSIOBSERVTER Folios: 59

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 17,090
FECHA : FEBRERO 27 DE 2008

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAG	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	115625	27/02/2008	266,000.00
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	115634	27/02/2008	2,000.00
ALBERTO DIAZ	CONSIGNACION	BANCO DE BOGOTA	062754387	115635	27/02/2008	63,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEMAS COMERCIALES	266,000.00
		TOTAL : $	266,000.00

SON: DOSCIENTOS SESENTA Y SEIS MIL PESOS

RESPONSABLE : _____

251

Industria y Comercio
SUPERINTENDENCIA

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-120228.

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCIÓN**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **582** DE

FECHA **30** DE **NOVIEMBRE DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR

LA LEY EXPIRA EL **27** DE **FEBRERO** DEL **2008.**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____ NO __X_____

252

Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctor:
Ian Raisbeck Llinas
Apoderado

Oficio N°: 5471

ASUNTO:

Radicación PCT Nº	06-120228
Trámite	011
Evento	379
Actuación	440
Folios	010

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por la doctora Eliana Isaura Moreno Bohórquez, en su calidad de apoderada de Procaps S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única Nº 10 de 2001.

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

El anterior oficio fue notificado por fijación en lista de fecha, 25 ABR. 2008.

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2020
Bogotá, D.C.,

Doctor:
Ian Raisbeck Llinas
Apoderado

Oficio N°: 5472

ASUNTO:

Radicación PCT Nº	06-120228
Trámite	011
Evento	379
Actuación	440
Folios	053

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado de Laboratorio Franco Colombiano Lafrancol S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única Nº 10 de 2001.

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SEÑOR
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
E. S. D.

REF: **Expediente 06-120-228**

TÍTULO SOLICITADO: **"TRATAMIENTO DE LA HEMORRAGIA DE DISRUPCIÓN EN REGÍMENES ANTICONCEPTIVOS EXTENDIDOS."**

PUBLICACIÓN: **Gaceta 582 de 30 de Noviembre de 2007, número de publicación 981.**

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SOLICITANTE: **SCHERING AKTIENGESELLSCHAFT**

APODERADO: **J. IAN RAISBECK**

TRÁMITE: **SUSTENTACION 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.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2º de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada en los siguientes términos:

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I. RATIFICACIÓN

Comedidamente me permito insistir en los argumentos planteados en la oposición respectiva, los cuales, como se dijo en su momento, demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los artículos 14, 16, 18 y 20 d) de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario, veamos:

- La combinación de estrógenos y progestanos en regímenes monofásicos y cantidades que permitan disminuir ciertos efectos adversos, como las hemorragias y afecciones andrógenas se encuentra revelado en la literatura científica tal como se muestra en los siguientes documentos:

  - Use Of An Oral Contraceptive Containing Drospirenone In An Extended Regimen[1].
  - Attitude Of German Women And Gynecologists Towards Long-Cycle Treatment With Oral Contraceptives[2].
  - An Open-Label, Multicenter, Noncomparative Safety And Efficacy Study Of Mircette, A Low-Dose Estrogen-Progestin Oral Contraceptive. The Mircette Study Group[3].
  - Selectivity and minimal androgenicity of norgestimate in monophasic and triphasic oral contraceptives[4].

- La publicación internacional WO 02/22110 publicada el 21 de Marzo de 02 y titulada "CONTRACEPTION PROCESS AND ADMINISTRATION FORM FOR THE SAME" revela , no solo el uso de la combinación de un estrógeno y un progestágeno (etinil estradiol, estradiol, acetato de ciproterona, desogestrel,

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[1] Use of an oral contraceptive containing drospirenone in an extended regimen. (eng; includes abstract) By Sillem M, The European Journal Of Contraception & Reproductive Health Care: The Official Journal Of The European Society Of Contraception [Eur J Contracept Reprod Health Care], 2003 Sep; Vol. 8 (3), pp. 162-9; PMID: 14667328.

[2] Attitude of German women and gynecologists towards long-cycle treatment with oral contraceptives. By: Wiegratz, I.; Hommel, H.H.; Zimmermann, T.; Kuhl, H., Contraception, Jan2004, Vol. 69 Issue 1, p37, 6p; DOI: 10.1016/j.contraception.2003.09.004; (AN 11885388)

[3] An open-label, multicenter, noncomparative safety and efficacy study of Mircette, a low-dose estrogen-progestin oral contraceptive. The Mircette Study Group. (eng; includes abstract), American Journal Of Obstetrics And Gynecology [Am J Obstet Gynecol], 1998 Jul; Vol. 179 (1), pp. S2-8; PMID: 9704812.

[4] Selectivity and minimal androgenicity of norgestimate in monophasic and triphasic oral contraceptives. (eng; includes abstract) By Anderson FD, Acta Obstetricia Et Gynecologica Scandinavica. Supplement [Acta Obstet Gynecol Scand Suppl], 1992; Vol. 156, pp. 15-21; PMID: 1324552

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dienogest, gestodeno, levonorgestrel, norgestimato, norgestrel y drospirenona- como los mencionados en la solicitud en trámite), para la obtención de un método de contracepción que puede ser beneficioso en caso de presentarse alguna sintomatología molesta para la mujer (tipo hemorragias), sino que dicho método contraceptivo, al igual que el de la solicitud colombiana en tramite, incluye un periodo donde se suspende la toma de los compuestos activos (que puede darse a través de placebos) y, tanto en el intervalo de tiempo que puede durar dicho periodo donde se suspende la toma, como en el tiempo del intervalo de toma posterior a dicha suspensión.

- La patente americana US 03/0119798 publicada el 26 de junio de 03 y titulada "PHARMACEUTICAL COMPOSITION FOR USE AS A CONTRACEPTIVE" revela claramente el uso de drospirenona y etinil estradiol, dos de los principios activos mencionados por la solicitud colombiana en trámite, en rangos de cantidades que incluyen a los mencionados por la misma, en formulaciones farmacéuticas contraceptivas para administración oral diaria que incluyen un intervalo de suspensión de la toma que involucra la toma de placebos y proporcionan un método para disminuir las hemorragias y los trastornos andrógenos (acné), tal como se menciona en las reivindicaciones 2, 39, 40, 41, 47 y 54.

- La patente americana US 6,451,778 publicada el 17 de septiembre de 02 y titulada "ORAL CONTRACEPTIVE" revela el empleo de varios de los principios activos mencionados por la solicitud colombiana en trámite (etinil estradiol, drospirenona, dienogest y trimegestone), en rangos de cantidades que incluyen a los mencionados por la misma, en formulaciones farmacéuticas contraceptivas para administración oral diaria que incluyen un intervalo de suspensión de la toma que involucra la toma de placebos y que proporcionan un método contraceptivo monofásico para disminuir los efectos adversos, característica mencionada en las reivindicaciones 1, 2, 39, 40, 41 y 47.

- La publicación internacional WO 98/04269 publicada el 05 de febrero de 1998 y titulada "MONOPHASIC CONTRACEPTIVE METHOD AND KIT COMPRISING A COMBINATION OF A PROGESTIN AND ESTROGEN" revela el uso de varios de los principios activos mencionados por la solicitud colombiana en trámite (etinil estradiol, drospirenona, dienogest y

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trimegestone), en rangos de cantidades que incluyen a los mencionados por la misma, en formulaciones farmacéuticas contraceptivas para administración oral diaria que incluyen un intervalo de suspensión de la toma que involucra la toma de placebos. Además dichas formulaciones proporcionan un método contraceptivo monofásico para disminuir los efectos adversos, característica fundamental para la solicitud colombiana en trámite y que se menciona explícitamente en las reivindicaciones 1, 2, 39, 40, 41 y 47.

- La simple lectura del capítulo reivindicatorio de la solicitud colombiana en trámite, pretende sin más, y sin que sea dado hacer interpretaciones extensivas, obtener exclusividad sobre un método de tratamiento, tal como lo menciona el contenido de sus reivindicaciones 1 a 54; pretensión que es inaceptable de acuerdo con las normas vigentes, ya que explícitamente en el articulo 20 literal d) de la decisión 486 se expresa que *"No serán patentables: Los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnostico aplicados a los seres humanos o animales."*

II. COMPLEMENTO DE INFORMACIÓN

2.1 A continuación se exponen varias publicaciones científicas en donde se evidencia de manera clara la existencia anticipada del uso de varios de los compuestos mencionados por la solicitud colombiana en trámite en el tratamiento de síntomas premenstruales, de PMDD, endometriosis, dismenorrea y PCOS, desvirtuando consecuentemente el nivel inventivo de la misma, en especial de sus reivindicaciones 50 a 55, veamos:

- **Therapy Of Endometriosis With Dienogest[5].**

Abstract:

Dienogest (17 alpha-cyanomethyl-17 beta-hydroxy-estra-4,9-dien-3-one, VEB Jenapharm, Jena, GDR), an orally active 19-nortestosterone derivative, was used firstly in the treatment of endometriosis. 57 patients (age 17-45 years) have been entered into the study. The diagnosis was confirmed by laparoscopy or laparotomy in 56 cases and in one case clinically. All patients have been treated with 2 mg dienogest per day in a progestin only regimen over a period of 6 month. The day after completing the course of dienogest therapy 51 patients underwent laparoscopy for control. On this basis endometriotic lesions had

[5] Köhler G, Göretzlehner G, Amon I. Zentralbl Gynakol. 1987;109(12):795-801.

completely disappeared in 66.7%; in 80.4% a marked improvement was noted, but no effect was visible in 19.6% of the implants. Eighty-four per cent of the women reported symptomatic improvement. The efficacy of dienogest was correlated negative with the age of the treated women. The major side effects were spottings and decrease of libido. Blood pressure as well as mean body weight remained unaltered. No patient discontinued dienogest therapy due to side effects.

- **A Levonorgestrel-Releasing Intrauterine System For The Treatment Of Dysmenorrhea Associated With Endometriosis: A Pilot Study[6].**

Abstract:

OBJECTIVE: To evaluate the efficacy and safety of an intrauterine system releasing 20 microg of levonorgestrel per 24 hours in the long-term treatment of recurrent dysmenorrhea in women already operated on conservatively for endometriosis. DESIGN: A prospective noncomparative pilot study. SETTING: A tertiary care and referral academic center for patients with endometriosis. PATIENT(S): Twenty parous women with recurrent moderate or severe dysmenorrhea after conservative surgery for endometriosis who did not want further children. INTERVENTION(S): A levonorgestrel-releasing intrauterine system was inserted in each woman within 7 days of the start of a menstrual cycle. MAIN OUTCOME MEASURE(S): Variations in severity of dysmenorrhea during treatment according to a 100-mm visual analogue scale and a 0-3-point verbal rating scale, modification of a pictorial blood-loss assessment chart devised to evaluate the amount of menstrual flow, and degree of satisfaction after 12 months of therapy. RESULT(S): One woman was lost to follow-up after achieving amenorrhea and expressing satisfaction, and 1 requested system removal because of weight gain and abdominal bloating. In another subject, the levonorgestrel intrauterine system was expelled 3 months after insertion. The menstrual patterns in the remaining 17 women were characterized by amenorrhea in 4 cases, hypomenorrhea or spotting in 8, and normal flow in 5. Baseline and 12-month follow-up mean +/- SD blood loss scores were 111+/-36 and 27+/-26, respectively. At the same time, mean +/- SD visual analogue and verbal rating scale scores dropped, respectively, from 76+/-12 to 34+/-23 points and from 2.5+/-0.5 to 1.2+/-0.5 points. Four women were very satisfied with treatment, 11 were satisfied, 2 were uncertain, and 3 were dissatisfied at 12-month follow-up. CONCLUSION(S): Because of the amenorrhea or hypomenorrhea induced in most women, a levonorgestrel intrauterine system greatly reduced menstrual pain associated with endometriosis and achieved a high degree of patient satisfaction.

- **Comparison Of Transdermal Estradiol And Tibolone For The Treatment Of Oophorectomized Women With Deep Residual Endometriosis[7].**

Abstract:

STUDY OBJECTIVE: To compare the effect of HRT with transdermal estradiol and that of treatment with tibolone in post-menopausal women with residual endometriosis. MATERIALS AND METHODS: 21 women with residual pelvic endometriosis after bilateral oophorectomy with or without hysterectomy were enrolled in the study and were randomized to HRT with transdermal estradiol 50 mg twice weekly (n = 10) associated with cyclic medroxyprogesterone acetate 10

[6] Vercellini P, Aimi G, Panazza S, De Giorgi O, Pesole A, Crosignani PG. Fertil Steril. 1999 Sep;72(3):505-8.
[7] Fedele L, Bianchi S, Raffaelli R, Zanconato G. Maturitas. 1999 Aug 16;32(3):189-93.

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mg daily in women who preserved uterus, and to treatment with tibolone 2.5 mg administered orally once a day (n = 11). The duration of both treatments was scheduled to last at least 12 months. Residual endometriosis was located in the bowel wall in four patients, in the rectovaginal septum in six and deeply in the retroperitoneal pelvic space in six. All women were symptomatic before oophorectomy. RESULTS: All the women were followed for 12 months. No patient suspended therapy because of side effects. Four patients of the estradiol group experienced moderate pelvic pain during treatment compared with only one patient in the tibolone group. One patient in the estradiol group reported severe dyspareunia. CONCLUSION: Although our series is very small, it seems that tibolone may be a safe hormonal treatment for post-menopausal women with residual endometriosis.

- **Evaluation of a unique oral contraceptive in the treatment of premenstrual dysphoric disorder.**[8]

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 microg) 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.

- **Lipid Metabolic Studies In Women With A Polycystic Ovary Syndrome During Treatment With A Low-Dose Desogestrel-Ethinylestradiol Combination**[9].

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[8] Freeman EW, Kroll R, Rapkin A, Pearlstein T, Brown C, Parsey K, Zhang P, Patel H, Foegh M; PMS/PMDD Research Group. J Womens Health Gend Based Med. 2001 Jul-Aug;10(6):561-9.Related Articles, Links.

[9] Cullberg G, Hamberger L, Mattsson LA, Mobacken H, Samsioe G. Acta Obstet Gynecol Scand. 1985;64(3):203-7.

Abstract:

Twenty women with the polycystic ovary syndrome (PCO) were treated with a combination of desogestrel and ethinylestradiol (EE) and the effects on lipids and lipoproteins were compared with those induced in a group of 13 regularly menstruating, healthy women. All women were examined before and after 3 months of treatment. Compared with the regularly menstruating women, the PCO women had significantly higher body weights and blood pressure as well as elevated levels of triglycerides in serum and VLDL. During treatment, 14 out of 20 women affected by PCO lost weight. No significant change in blood pressure was observed. In the PCO group, moderate increments were encountered in serum cholesterol, phospholipids and triglycerides. No significant changes were seen in LDL-cholesterol or HDL-cholesterol. The ratio LDL-cholesterol/HDL-cholesterol did not alter. The level of total cholesterol in VLDL rose during treatment. These changes in serum and lipoprotein lipids in PCO patients were of the same type and magnitude as those found in the control group, apart from an increase in HDL-cholesterol in the latter. The only remaining difference after treatment was a slightly higher level of VLDL triglycerides in the PCO women. Thus only moderate changes were induced in lipid and lipoprotein patterns by the combination of desogestrel and EE. A "positive" influence on lipids and lipoproteins cannot be considered as a further advantage, added to the list of indications when hormonal treatment is used in PCO-affected women. The clinical implications of elevated triglycerides remain to be clarified.

- **Modificazione Dei Livelli Plasmatici Degli Androgeni E Della SHBG In Pazienti Con Sindrome Dell'ovaio Policistico (Pcos) Trattate Con Contraccettivi Orali Contenenti Desogestrel[10].**

Abstract:

8 women, aged 17-25, with polycystic ovary syndrome (PCO) were treated with Practil 21 (Organon) containing 30 mcg of ethinyl estradiol and 150 mcg of desogestrel, or with Planum (Menarini). Checkups were conducted 3 and 6 months later to measure hormone levels. The average level of testosterone dropped significantly from 121.5 (+ or - 50.9) ng/dl to 23.1 (+ or - 10.6) ng/dl after 3 months. The level of androstenedione also decreased significantly from 265.2 (+ or - 101.4) ng.dl to 96.7 (+ or - 22.5) ng/dl. Similarly, the level of 17-hydroxyprogesterone declined from 120.5 (+ or - 69.8) ng/dl to 24.5 (+ or - 10.7) ng/dl . On the other hand, the level of sex hormone binding globulin rose from 1.3 (+ or - .6) mcg/100 ml to 3.9 (+ or - 1.8) mcg/100 ml. Cortisone level increased significantly from 15 (+ or - 3.2) mcg/100 ml to 30.6 (+ or - 10.4) mcg/100 ml after 3 months, but the normal range (5-20 mcg/100 ml) was attained at the end. Ecographic evaluation of the size of the ovaries indicated a 18.2-66.5% reduction after 3 months. In 3 cases, the number and dimension of follicles also diminished conspicuously. Acne, hirsutism, and other symptoms of hyperandrogenism also declined. Side effects were minor and included slight weight gain, spotting and headache; treatment was suspended in only 1 case because of a grand mal seizure. The administration of this new monophasic OC proved to be a valid alternative therapy for PCO.

- **Primary Dysmenorrhea Treatment With A Desogestrel-Containing Low-Dose Oral Contraceptive[11].**

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[10] Negri P. D'Errico G. Minisci N. Tomasi A. Minerva Ginecologica. 40(12):699-707, 1988 Dec.
[11] Hendrix SL, Alexander NJ. Contraception. 66(6):393-9, 2002 Dec.

Abstract:

This randomized, double-blind, placebo-controlled exploratory study examined the efficacy and safety of a low-dose oral contraceptive (Mircette), desogestrel/ethinyl estradiol [DSG/EE] and ethinyl estradiol [EE]) in relieving the symptoms of dysmenorrhea. Twenty-three clinics in the United States enrolled 77 women (age < or =32 years) with primary dysmenorrhea documented for at least four consecutive cycles. Forty participants received DSG/EE&EE and 37 received placebo for four consecutive 28-day cycles. The intensity of menstrual-related distress was measured with the Menstrual Distress Questionnaire (MDQ). Patient diaries were used to assess number of school/work days missed as well as the use of rescue medication. Participants receiving DSG/EE&EE recorded reduced menstrual pain severity, lower total MDQ scores, and significantly less menstrual cramping. No significant change in bloating, anxiety, loneliness, weight gain, or acne was reported. The DSG/EE&EE formulation shows promise for the treatment of primary dysmenorrhea and was well tolerated by the participants in this study.

- **Relief Of Essential Dysmenorrhea With Ethinyl Estradiol[12].**

Abstract:

The efficacy of ethinyl estradiol (EE) treatment of essential dysmenorrhea was studied in 12 patients over 138 cycles. 50 mcg/day EE was administered at least 21 days prior to expected menstruation for 44 treatment cycles. The therapy effectively inhibited ovulation and relieved dysmenorrhea. There were 6 amenorrheic cycles in which withdrawal of EE resulted in dysmenorrhea. There were no instances of nausea or toxic sequelae, and the treatment was well tolerated by the patients. For the time, discontinuation of treatment is recommended for 1 cycle if 2 successive, successful treatment cycles occur.

- **The Relation Between Obesity And Testosterone-Estradiol Binding Globulin Levels In Polycystic Ovarian Syndrome (PCO)[13].**

Abstract:

Serum testosterone-estradiol binding globulin levels (TEBG), total and free testosterone levels, were evaluated in 36 patients with polycystic ovarian syndrome (PCO), and nine volunteers with normal cycles. TEBG concentration was markedly reduced in all PCO patients in comparison to the controls. However, the difference between the means was statistically significant for the obese PCO patients only. The serum free testosterone levels were elevated in all PCO patients, although the total testosterone levels were normal in 42.8% of obese and 13.3% of nonobese patients. It is suggested that obesity is a factor in causing reduction of TEBG levels. Also, it might be a contributory factor in the etiology of PCO.

- **Ultrasound Study Of Ovarian And Uterine Morphology In Women With Polycystic Ovary Syndrome Before, During And After Treatment With Cyproterone Acetate And Ethinyloestradiol[14].**

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[12] Lyon RA. Surgery Gynecology and Obstetrics. 1943;77:657-660.

[13] Badawy SZ, Weigert JM, Marshall LD, Cuenca VG. Diagn Gynecol Obstet. 1980 Spring;2(1):43-6.

[14] S. Venturoli , R. Paradisi, E. Saviotti, E. Porcu, R. Fabbri, L. F. Orsini, L. Bovicelli and C. Flamigni. Archives of Gynecology and Obstetrics. Volume 237, Number 1 / agosto de 1985.

Abstract:

Women with the polycystic ovary syndrome were treated cyclically for two years with an oral oestrogen/progestogen combination of 50 mg of cyproterone acetate and 0.05 mg of ethinyloestradiol. Ovarian volume, ovarian texture and uterine size were monitored by ultrasound before, during and after treatment. Menstrual rhythm, ovulation and the degree of hirsutism were also studied clinically. A significant decrease in the ovarian volume and in the number of cystic areas was observed during treatment. Hirsutism was also markedly improved. Some of these beneficial effects persisted after treatment was stopped. The number of subjects who had regular, ovulatory cycles increased after stopping treatment. Growth of uterine muscle occurred during treatment.

- **Use Of A Levonorgestrel-Releasing Intrauterine Device In The Treatment Of Rectovaginal Endometriosis[15].**

Abstract:

OBJECTIVE: To evaluate the effectiveness of a levonorgestrel-releasing IUD as therapy for endometriosis of the rectovaginal septum. DESIGN: Prospective therapeutic non-randomized, self-controlled clinical trial analyzing changes in pain symptoms and size of lesions induced by the levonorgestrel-releasing IUD over 12 months. SETTING: Tertiary referral center for treatment of deep endometriosis. PATIENT(S): Eleven symptomatic patients with rectovaginal endometriosis. INTERVENTION(S): A levonorgestrel-releasing IUD was inserted and maintained for 12 months. MAIN OUTCOME MEASURE(S): Severity of dysmenorrhea, pelvic pain, and deep dyspareunia were assessed before insertion of the IUD and throughout treatment. The size of rectovaginal endometriotic lesions were evaluated by using transrectal and transvaginal ultrasonography. RESULT(S): Dysmenorrhea, pelvic pain, and deep dyspareunia greatly improved and the size of the endometriotic lesions was significantly reduced by treatment. CONCLUSION(S): Insertion of a levonorgestrel-releasing IUD alleviates pain and reduces the size of lesions in patients with endometriosis of the rectovaginal septum.

Como se observa, los principios activos mencionados a lo largo de todos estos artículos científicos y su uso en los trastornos allí consignados, demuestran nuevamente la falta de nivel inventivo de la solicitud colombiana en trámite en tanto que la composición farmacéutica de la solicitud en trámite al contener dichos principios activos puede ayudar evidentemente a mejorar la sintomatología de dichos trastornos que ya previamente habían sido atendidos y manejados.

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales y que en consecuencia se decrete, además de la negación de la solicitud en comento, el archivo del expediente que la contiene.

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[15] Fedele L, Bianchi S, Zanconato G, Portuese A, Raffaelli R. Fertility and sterility. 75(3):485-8, 2001 Mar.

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1: Zentralbl Gynakol. 1987;109(12):795-801.

[Therapy of endometriosis with dienogest]

(Article in German)

Kötzger G, Gmeiner G, Amon J.

Dienogest (17 alpha-cyanomethyl-17 beta-hydroxy-estra-4,9-dien-3-one, VEB Jenapharm, Jena, GDR), an orally active 19-nortestosterone derivative, was used firstly in the treatment of endometriosis. 97 patients (age 17-45 years) have been entered into the study. The diagnosis was confirmed by laparoscopy or laparotomy in 56 cases and in one case clinically. All patients have been treated with 2 mg dienogest per day in a progestin only regimen over a period of 6 month. The day after completing the course of dienogest therapy 51 patients underwent laparoscopy for control. On this basis endometriotic lesions had completely disappeared in 66.7%; in 30.4% a marked improvement was noted, but no effect was visible in 19.6% of the implants. Eighty-four per cent of the women reported symptomatic improvement. The efficacy of dienogest was correlated negative with the age of the treated women. The major side effects were spottings and decrease of libido. Blood pressure as well as mean body weight remained unaltered. No patient discontinued dienogest therapy due to side effects.

PMID: 3503463 [PubMed - indexed for MEDLINE]

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1: Fertil Steril. 1999 Sep;72(3):505-8.

A levonorgestrel-releasing intrauterine system for the treatment of dysmenorrhea associated with endometriosis: a pilot study.

Vercellini P, Aimi G, Panazza S, De Giorgi O, Pesole A, Crosignani PG.

Clinica Ostetrica e Ginecologica Luigi Mangiagalli, University of Milano, Italy. pgcros@imlucca.unimi.it

OBJECTIVE: To evaluate the efficacy and safety of an intrauterine system releasing 20 microg of levonorgestrel per 24 hours in the long-term treatment of recurrent dysmenorrhea in women already operated on conservatively for endometriosis. DESIGN: A prospective noncomparative pilot study. SETTING: A tertiary care and referral academic center for patients with endometriosis. PATIENT(S): Twenty parous women with recurrent moderate or severe dysmenorrhea after conservative surgery for endometriosis who did not want further children. INTERVENTION(S): A levonorgestrel-releasing intrauterine system was inserted in each woman within 7 days of the start of a menstrual cycle. MAIN OUTCOME MEASURE(S): Variations in severity of dysmenorrhea during treatment according to a 100-mm visual analogue scale and a 0-3-point verbal rating scale, modification of a pictorial blood-loss assessment chart devised to evaluate the amount of menstrual flow, and degree of satisfaction after 12 months of therapy. RESULT(S): One woman was lost to follow-up after achieving amenorrhea and expressing satisfaction, and 1 requested system removal because of weight gain and abdominal bloating. In another subject, the levonorgestrel intrauterine system was expelled 3 months after insertion. The menstrual patterns in the remaining 17 women were characterized by amenorrhea in 4 cases, hypomenorrhea or spotting in 8, and normal flow in 5. Baseline and 12-month follow-up mean +/- SD blood loss scores were 111+/-36 and 27+/-26, respectively. At the same time, mean +/- SD visual analogue and verbal rating scale scores dropped, respectively, from 78+/-12 to 34+/-23 points and from 2.5+/-0.5 to 1.2+/-0.5 points. Four women were very satisfied with treatment, 11 were satisfied, 2 were uncertain, and 3 were dissatisfied at 12-month follow-up. CONCLUSION(S): Because of the amenorrhea or hypomenorrhea induced in most women, a levonorgestrel intrauterine system greatly reduced menstrual pain associated with endometriosis and achieved a high degree of patient satisfaction.

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1: Maturitas. 1999 Aug 10;32(2):189-93.

Comparison of transdermal estradiol and tibolone for the treatment of oophorectomized women with deep residual endometriosis.

Pellicà L, Mioretti S, Raffaelli R, Zanconato G.

Department of Obstetrics and Gynecology, University of Verona, Policlinico Borgoroma, Italy. obgyn@veniel.it

STUDY OBJECTIVE: To compare the effect of HRT with transdermal estradiol and that of treatment with tibolone in post-menopausal women with residual endometriosis. MATERIALS AND METHODS: 21 women with residual pelvic endometriosis after bilateral oophorectomy with or without hysterectomy were enrolled in the study and were randomized to HRT with transdermal estradiol 50 mg twice weekly (n = 10) associated with cyclic medroxyprogesterone acetate 10 mg daily in women who preserved uterus, and to treatment with tibolone 2.5 mg administered orally once a day (n = 11). The duration of both treatments was scheduled to last at least 12 months. Residual endometriosis was located in the bowel wall in four patients, in the rectovaginal septum in six and deeply in the retroperitoneal pelvic space in six. All women were symptomatic before oophorectomy. RESULTS: All the women were followed for 12 months. No patient suspended therapy because of side effects. Four patients of the estradiol group experienced moderate pelvic pain during treatment, contrasted with only one patient in the tibolone group. One patient in the estradiol group reported severe dyspareunia. CONCLUSION: Although our series is very small, it seems that tibolone may be a safe hormonal treatment for post-menopausal women with residual endometriosis.

PMID: 10515074 [PubMed - indexed for MEDLINE]

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Drospirenone OC May Relieve Some PMDD Symptoms

A new oral contraceptive (OC) on the U.S. market contains 30 µg of ethinyl estradiol and 3 mg of drospirenone (DRSP), a progestin (see *JWWH* Jul 2000, p. 51, accession number 000701005, and *Contraception* 2000; 61:105). Because DRSP is an analogue of spironolactone, it has antiandrogenic and antimineralocorticoid effects, suggesting that it, like the diuretic spironolactone, may benefit women with premenstrual dysphoric disorder (PMDD). To test this hypothesis, these authors conducted a multicenter, double-blind, partially manufacturer-supported study in which 82 healthy, ovulating women (aged 18-40) who met DSM-IV PMDD criteria were randomized to receive the new OC or placebo for 3 months.

Symptoms were measured at baseline and throughout the study using the Calendar of Premenstrual Experiences (COPE). Women made daily phone calls to report their emotional symptoms (factor 1); physical symptoms, including fatigue, dizziness, hot flashes, palpitations, headaches, and nausea (factor 2); acne, appetite, and food cravings (factor 3); and fluid-retention symptoms (factor 4). The groups were demographically similar and predominantly white.

Fifty percent of OC users and 30 percent of placebo users had discontinued treatment by the end of the third cycle. The OC group showed greater improvement from baseline in all 4 COPE factors than did the placebo group; however, the only statistically significant difference between the groups in level of improvement was seen in factor 3. As in other PMDD studies, there was a high placebo-response rate (43 percent), which the authors suggested might be due to a therapeutic effect of daily symptom reporting.

Comments: This study was placebo-controlled; however, its findings are limited by the examination of only 3 cycles of use and by a high dropout rate (particularly in the OC group, suggesting that these women were unblinded during the study); in addition, one of the authors is employed by the OC manufacturer. Significant improvement occurred only in factor 3 symptoms, which may be caused by androgen and relieved by this antiandrogenic formulation. I would not recommend the DSRP OC as a first-line treatment for PMDD; however, it may be a good choice for women who need contraception and who have factor 3 symptoms.

— DE Judge

Published in Journal Watch Women's Health *October 31, 2001*

Citation(s):

Freeman EW et al. Evaluation of a unique oral contraceptive in the treatment of premenstrual dysphoric disorder. *J Womens Health Gend Based Med* 2001 Jul-Aug; 10:561-569.

Medline abstract (Free).

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J Womens Health Gend Based Med. 2001 Jul-Aug;10(6):561-9.

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- J Womens Health Gend Based Med. 2002 Mar;11(2):95-6.

Evaluation of a unique oral contraceptive in the treatment of premenstrual dysphoric disorder.

Freeman EW, Kroll R, Rapkin A, Pearlstein T, Brown C, Parsey K, Zhang P, Patel H, Foegh M; PMS/PMDD Research Group.

Department of Obstetrics/Gynecology, University of Pennsylvania, Philadelphia, PA, USA.

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 microg) 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 (POMS), 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.

Publication Types:

- Clinical Trial
- Multicenter Study
- Randomized Controlled Trial

PMID: 11559453 [PubMed - indexed for MEDLINE]

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1: Acta Obstet Gynecol Scand. 1985;64(3):203-7.

Lipid metabolic studies in women with a polycystic ovary syndrome during treatment with a low-dose desogestrel-ethinylestradiol combination.

Cullhorg G, Hamberger L, Mattsson LA, Nobelius H, Ramstedt G.

Twenty women with the polycystic ovary syndrome (PCO) were treated with a combination of desogestrel and ethinylestradiol (EE) and the effects on lipids and lipoproteins were compared with those induced in a group of 13 regularly menstruating, healthy women. All women were examined before and after 3 months of treatment. Compared with the regularly menstruating women, the PCO women had significantly higher body weights and blood pressure as well as elevated levels of triglycerides in serum and VLDL. During treatment, 14 out of 20 women affected by PCO lost weight. No significant change in blood pressure was observed. In the PCO group, moderate increments were encountered in serum cholesterol, phospholipids and triglycerides. No significant changes were seen in LDL-cholesterol or HDL-cholesterol. The ratio LDL-cholesterol/HDL-cholesterol did not alter. The level of total cholesterol in VLDL rose during treatment. These changes in serum and lipoprotein lipids in PCO patients were of the same type and magnitude as those found in the control group, apart from an increase in HDL-cholesterol in the latter. The only remaining difference after treatment was a slightly higher level of VLDL triglycerides in the PCO women. Thus only moderate changes were induced in lipid and lipoprotein patterns by the combination of desogestrel and EE. A "positive" influence on lipids and lipoproteins cannot be considered as a further advantage, added to the list of indications when hormonal treatment is used in PCO-affected women. The clinical implications of elevated triglycerides remain to be clarified.

PIP: 20 women with the polycystic ovary syndrome (PCO) were treated with a combination of desogestrel and ethinylestradiol (EE) and the effects on lipids and lipoproteins were compared with those induced in a group of 13 regularly menstruating, healthy women. All women were examined before and after 3 months of treatment. Compared with the regularly menstruating women, the PCO women had significantly higher body weights and blood pressure as well as elevated levels of triglycerides in serum and VLDL. During treatment, 14 out of 20 women affected by PCO lost weight. No significant change in blood pressure was observed. In the PCO group, moderate increments were encountered in serum cholesterol, phospholipids, and triglycerides. No significant changes were seen in LDL-cholesterol or HDL-cholesterol. The ratio LDL-cholesterol/HDL-cholesterol did not alter. The level of total cholesterol in VLDL rose during treatment. These changes in serum and lipoprotein lipids in PCO patients were of the same type and magnitude as those found in the control group, apart from an increase in HDL-cholesterol in the latter. The only remaining difference after treatment was a slightly level of VLDL triglycerides in the PCO women. Thus only moderate changes were induced in lipid and lipoprotein patterns by the combination of desogestrel and EE. A "positive" influence on lipids and lipoproteins cannot be considered as a further advantage, added to the list indications when hormonal treatment is used in PCO-affected women. The clinical implications of elevated triglycerides remain to be clarified.

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Modificazione dei livelli plasmatici degli androgeni e della SHBG in pazienti con sindrome dell'ovaio policistico (PCOs) trattate con contraccettivi orali contenenti desogestrel. [Changes in plasma levels of androgens and SHBG in patients with polycystic ovary syndrome (PCOs) treated with oral contraceptives containing desogestrel].

Negri P, D'Errico G, Minisci N, Tomasi A

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Title	[Changes in plasma levels of androgens and SHBG in patients with polycystic ovary syndrome (PCOs) treated with oral contraceptives containing desogestrel]. [Italian]
Original Title	Modificazione dei livelli plasmatici degli androgeni e della SHBG in pazienti con sindrome dell'ovaio policistico (PCOs) trattate con contraccettivi orali contenenti desogestrel.
Source	Minerva Ginecologica. 40(12):699-707, 1988 Dec.
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Journal Subset: IM, J

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MeSH Subject Headings:
Adolescent;
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*Androgens / bl [Blood];
Androstenedione / bl [Blood];
Contraceptives, Oral / tu [Therapeutic Use];
Desogestrel;
Drug Combinations;
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*Progesterone Congeners / tu [Therapeutic Use];
*Sex Hormone-Binding Globulin / an [Analysis];
Testosterone / bl [Blood]

Keyword Heading: Androgens: Biology; Contraception; Contraceptive Agents, Estrogen--administration and dosage; Contraceptive Agents, Female--administration and dosage; Contraceptive Agents, Progestin--administration and dosage; Contraceptive Agents--administration and dosage; Contraceptive Methods--beneficial effects; *Desogestrel--administration and dosage; Developed Countries; *Diseases; Endocrine System; *Ethinyl Estradiol--administration and dosage; Europe; Family Planning; *Hormones; Italy; Mediterranean Countries; *Oral Contraceptives, Low-dose--beneficial effects; Oral Contraceptives--beneficial effects; *Ovarian Cysts; Physiology; Southern Europe; *Testosterone; *Treatment.

Other Abstract: 8 women, aged 17-25, with polycystic ovary syndrome (PCO) were treated with Practil 21 (Organon) containing 30 mcg of ethinyl estradiol and 150 mcg of desogestrel, or with Planum (Menarini). Checkups were conducted 3 and 6 months later to measure hormone levels. The average level of testosterone dropped significantly from 121.8 (+ or - 50.9) ng/dl to 23.1 (+ or - 10.4) ng/dl after 3 months. The level of androstenedione also decreased significantly from 265.2 (+ or - 101.4) ng/dl to 96.7 (+ or - 22.8) ng/dl. Similarly, the level of 17-hydroxyprogesterone

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declined from 120.5 (+ or - 69.8) ng/dl to 24.5 (+ or - 10.7) ng/dl. On the other hand, the level of sex hormone binding globulin rose from 1.3 (+ or - .6) mcg/100 ml to 2.9 (+ or - 1.8) mcg/100 ml. Cortisone level increased significantly from 15 (+ or - 3.2) mcg/100 ml to 30.6 (+ or - 10.4) mcg/100 ml after 3 months, but the normal range (5-20 mcg/100 ml) was attained at the end. Ecographic evaluation of the size of the ovaries indicated a 16.2-66.5% reduction after 3 months. In 3 cases, the number and dimension of follicles also diminished conspicuously. Acne, hirsutism, and other symptoms of hyperandrogenism also declined. Side effects were minor and included slight weight gain, spotting and headache; treatment was suspended in only 1 case because of a grand mal seizure. The administration of this new monophasic OC proved to be a valid alternative therapy for PCO.

General Note	T.I.: MINERVA GINECOLOGICA. ?
CAS Registry/EC Number/Name of Substance	0 (Androgens). 0 (Contraceptives, Oral). 0 (Drug Combinations). 0 (Hydroxyprogesterones). 0 (Norpregnenes). 0 (Progesterone Congeners). 0 (Sex Hormone-Binding Globulin). 5-0224-27-8 (Desogestrel). 57-63-6 (Ethinyl Estradiol). 58-22-0 (Testosterone). 63-05-8 (Androstenedione).
ISSN Print	0026-4784
Publication Type	English Abstract. Journal Article.
Language	Italian
Date of Publication	1988 Dec
Entry Date	19890526
Revision Date	20061115
Update Date	20071203

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Primary dysmenorrhea treatment with a desogestrel-containing low-dose oral contraceptive.

Hendrix SL, Alexander NJ

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Accession Number	CN-00434848
Author	Hendrix SL, Alexander NJ
Institution	Wayne State University, Detroit, MI 48201, USA. shendrix@med.wayne.edu
Title	Primary dysmenorrhea treatment with a desogestrel-containing low-dose oral contraceptive.
Source	Contraception. 66(6):393-9, 2002 Dec.
Abstract	This randomized, double-blind, placebo-controlled exploratory study examined the efficacy and safety of a low-dose oral contraceptive (Mircette), desogestrel/ethinyl estradiol [DSG/EE] and ethinyl estradiol [EE]) in relieving the symptoms of dysmenorrhea. Twenty-three clinics in the United States enrolled 77 women (age < or =32 years) with primary dysmenorrhea documented for at least four consecutive cycles. Forty participants received DSG/EE&EE and 37 received placebo for four consecutive 28-day cycles. The intensity of menstrual-related distress was measured with the Menstrual Distress Questionnaire (MDQ). Patient diaries were used to assess number of school/work days missed as well as the use of rescue medication. Participants receiving DSG/EE&EE recorded reduced menstrual pain severity, lower total MDQ scores, and significantly less menstrual cramping. No significant change in bloating, anxiety, loneliness, weight gain, or acne was reported. The DSG/EE&EE formulation shows promise for the treatment of primary dysmenorrhea and was well tolerated by the participants in this study.
Publication	Clinical Trial, Journal Article, Randomized Controlled Trial.

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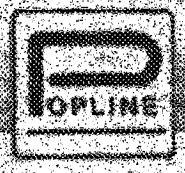
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Serials Code	00001203
Subject Headings	Humans Adult Female *Contraceptives, Oral, Synthetic/ad [Administration & Dosage] Contraceptives, Oral, Synthetic/ae [Adverse Effects] *Desogestrel/ad [Administration & Dosage] Desogestrel/ae [Adverse Effects] Double-Blind Method *Dysmenorrhea/dt [Drug Therapy] Ethinyl Estradiol/ad [Administration & Dosage] Headache/ci [Chemically Induced] Placebos Treatment Outcome United States
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1.
Title: Relief of essential dysmenorrhea with ethinyl estradiol.
Author: Lyon RA.
Source: Surgery Gynecology and Obstetrics. 1943;77:657-660.
Abstract: The efficacy of ethinyl estradiol (EE) treatment of essential dysmenorrhea was studied in 12 patients over 138 cycles. 50 mcg/day EE was administered at least 21 days prior to expected menstruation for 44 treatment cycles. The therapy effectively inhibited ovulation and relieved dysmenorrhea. There were 6 amenorrheic cycles in which withdrawal of EE resulted in dysmenorrhea. There were no instances of nausea or toxic sequelae, and the treatment was well tolerated by the patients. For the time, discontinuation of treatment is recommended for 1 cycle if 2 successive, successful treatment cycles occur.
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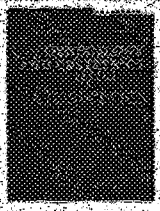
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Ultrasound study of ovarian and uterine morphology in women with polycystic ovary syndrome before, during and after treatment with cyproterone acetate and ethinyloestradiol

Publicación	Archives of Gynecology and Obstetrics
Editor	Springer Berlin / Heidelberg
ISSN	0932-0067 (Print) 1432-0711 (Online)
Fascículo/ejemplar/número	Volume 237, Number 1 / agosto de 1985
Categoría	Originals
DOI	10.1007/BF02133945
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S. Venturoli[1] ✉, R. Paradisi[1], E. Saviotti[1], E. Porcu[1], R. Fabbri[1], L. F. Orsini[2], L. Bovicelli[2] and C. Flamigni[1]

(1) Institute of Reproductive Physiology and Pathology, University of Bologna, Via Massarenti 13, I-40138 Bologna, Italy

(2) Chair of Prenatal Pathophysiology, University of Bologna, Via Massarenti 13, I-40138 Bologna, Italy

Received: 8 August 1984 Accepted: 21 May 1985

Summary Women with the polycystic ovary syndrome were treated cyclically for two years with an oral oestrogen/progestogen combination of 50 mg of cyproterone acetate and 0.05 mg of ethinyloestradiol. Ovarian volume, ovarian texture and uterine size were monitored by ultrasound before, during and after treatment. Menstrual rhythm, ovulation and the degree of hirsutism were also studied clinically. A significant decrease in the ovarian volume and in the number of cystic areas was observed during treatment. Hirsutism was also markedly improved. Some of these beneficial effects persisted after treatment was stopped. The number of subjects who had regular, ovulatory cycles increased after stopping treatment. Growth of uterine muscle occurred during treatment.

Key words Ultrasonography - Polycystic ovary syndrome - Hirsutism - Oestrogen/progestogen treatment - Cyproterone acetate

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Use of a levonorgestrel-releasing intrauterine device in the treatment of rectovaginal endometriosis.

Fedele L, Bianchi S, Zanconato G, Portuese A, Raffaelli R

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Institution	Department of Maternal and Child Health, Biology and Genetics, University of Verona, Verona, Italy. obgynclin@univr.it
Title	Use of a levonorgestrel-releasing intrauterine device in the treatment of rectovaginal endometriosis.
Source	Fertility and sterility. 75(3):485-8, 2001 Mar.
Abstract	OBJECTIVE: To evaluate the effectiveness of a levonorgestrel-releasing IUD as therapy for endometriosis of the rectovaginal septum. DESIGN: Prospective therapeutic non-randomized, self-controlled clinical trial analyzing changes in pain symptoms and size of lesions induced by the levonorgestrel-releasing IUD over 12 months. SETTING: Tertiary referral center for treatment of deep endometriosis. PATIENT(S): Eleven symptomatic patients with rectovaginal endometriosis. INTERVENTION(S): A levonorgestrel-releasing IUD was inserted and maintained for 12 months. MAIN OUTCOME MEASURE(S): Severity of dysmenorrhea, pelvic pain, and deep dyspareunia were assessed before insertion of the IUD and throughout treatment. The size of rectovaginal endometriotic lesions were evaluated by using transrectal and transvaginal ultrasonography. RESULT(S): Dysmenorrhea, pelvic pain, and deep dyspareunia greatly improved and the size of the endometriotic lesions was significantly reduced by treatment. CONCLUSION(S): Insertion of a levonorgestrel-releasing IUD

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alleviates pain and reduces the size of lesions in patients with endometriosis of the rectovaginal septum.

Publication Type	Clinical Trial, Controlled Clinical Trial, Journal Article
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Solicitud de Patente de Invención Titulada: "TRATAMIENTO DE LA HEMORRAGIA DE DISRUPCION EN REGIMENES ANTICONCEPTIVOS EXTEDIDOS".
Solicitantes: SCHERING AKTIENGESELLSCHAFT.
Nuestra Ref.: P2006/000231

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN EL ARTÍCULO 44 DE LA DECISION 486, GACETA No. 582

J. IAN RAISBECK, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad solicitante, respetuosamente me permito solicitar que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma, dando cumplimiento a lo establecido en el artículo 44 de la Decisión 486 de la comisión de la Comunidad Andina. Adjunto recibo por el monto de $210.000 pesos para cubrir la tasa correspondiente, según la Resolución No. 44372 del 26 de Diciembre de 2007.

Atentamente,

J. IAN RAISBECK
C.C. 79.376.996 de Bogotá
T.P. 135.799

Anexo: Recibo por $210.000 pesos