



Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: Expediente 07-070-612

TÍTULO SOLICITADO: FORMA FARMACOLÒGICA PERORAL SÒLIDA PARA LA ANTICONCEPCIÒN.

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TRÁMITE: REMISIÒN DE INFORMACIÒN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de la firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del C.S.J, obrando en nombre y representaciòn de **LABORATORIO FRANCO-COLOMBIANO, LAFRANCOL S.A.**, sociedad comercial constituida y vigente de acuerdo con las leyes de la Repùblica de Colombia, con domicilio y sede principal en Cali, de manera respetuosa, y con el propòsito de coadyuvar en la decisiòn que sobre la solicitud de patente de la referencia deberà adoptarse, por este escrito me permito remitir informaciòn fundamentada que demuestra que la solicitud en mencion exigidos por la Decisiòn 486 de 2000, y que por ello deberìa el Despacho abstenerse de concederle el privilegio de patente solicitado.

Ademàs de la defensa del orden jurìdico vigente en materia de propiedad industrial, el presente escrito se fundamenta en la necesidad de evitar que la

concesión de la solicitud vulnere la libre competencia, y restrinja el mercado farmacéutico en perjuicio de los consumidores colombianos.

I. FUNDAMENTOS DE LA OPOSICION

La solicitud en curso, que reivindica una forma farmacéutica oral sólida para la anticoncepción que contiene dienogest y etinil estradiol de liberación retardada carece por completo de los requisitos fundamentales para otorgársele el privilegio de patente de invención, tal y como lo demuestran los siguientes argumentos:

- 1.1 En primer lugar, y si tenemos en cuenta que la **combinación farmacológica entre etinil estradiol y dienogest**, es una combinación ampliamente reconocida, estudiada y utilizada en el estado de la técnica, útil en contracepción, es del caso hacer notar que irrefutablemente la novedad de la solicitud colombiana en trámite se ve afectada, veamos:

➤ **Effect Of Ethinyl Estradiol-Dienogest Combination On Serum Androgen Concentrations¹.**

Abstract: Antiandrogens or progestins with an antiandrogenic component usually have only a weak antigonadotropic activity. It is thus possible that the antiandrogenic effect on the cellular level is cancelled or at least reduced by an increased ovarian androgen production. The aim of the four submitted clinical studies of the progestin and antiandrogen dienogest alone (0.5-2 mg/day) or of a combined regimen of ethinylestradiol (0.03 mg) plus dienogest (2 mg) (EE/DNG) was to examine the influence on the serum androgen and SHBG concentrations as well as on the serum FSH, LH, progesterone and 17 beta-estradiol concentrations in young women. Like the progesterone derivatives, dienogest has a relatively low antigonadotropic activity. Inhibition of ovulation is mainly produced by peripheral mechanisms such as the reduction of preovulatory 17 beta-estradiol secretion. Dienogest alone has no significant effects on the serum SHBG and androgen concentrations. Unlike this, the combination of EE plus DNG markedly increases SHBG concentrations (to 2.1-3.7 fold the basal levels). The decrease in serum androgens with total testosterone (by 17 and 40%), free testosterone (by 48 and 54%) and dehydroepiandrosterone sulfate (by 51%) corresponds to the values shown in the literature for other oral contraceptives with modern progestins. EE/DNG does not affect the serum concentrations of 5 alpha-dihydrotestosterone (DHT), although the marker of the peripheral transformation from T to DHT, androstenediol glucuronide, is distinctly reduced (by 38%). In a double-blind comparison no differences are found between EE/DNG and a regimen combining 0.02 mg of ethinylestradiol and 0.150 mg of desogestrel. Solely the SHBG concentrations, with EE/DNG, as expected, are significantly higher. In a sequential regimen, dienogest, chlormadinone acetate and desogestrel (progestins without binding to SHBG) enhance the inhibitory effect of ethinylestradiol sulfonate on free testosterone, whereas norethindrone acetate and levonorgestrel (progestins with a strong binding to SHBG) reduce this effect of the estrogen significantly. These results exclude the possibility that

¹ Oettel M, Carol W, Gräser T, Klinger G, Mellinger U, Moore C, Schindler AE, Winkler UH. Zentralbl Gynakol. 1997;119(12):597-606.

the very distinct antiandrogenic effect of dienogest on a cellular level is neutralised or reduced by an increased systemic supply of androgen.

➤ **Double-Blind, Randomized, Placebo Controlled Study On The Effects Of The Monophasic Oral Contraceptive Containing 30 Micrograms Ethinyl Estradiol And 2.00 Mg Dienogest On The Hemostatic System².**

Abstract: Forty healthy female volunteers aged between 19 and 35 years (27.3 +/- 4.1 years) with normal menstrual cycles were included in a double-blind, randomized, placebo-controlled study to investigate the influence on the hemostatic system of an oral contraceptive containing 30 micrograms ethinyl estradiol in combination with 2.00 mg dienogest, which is a 19-norprogesterone without a 17 alpha-ethinyl group. At baseline and during one treatment cycle, 12 hemostatic parameters were measured on cycle days 7, 14, and 21. The hemostatic parameters were categorized as either procoagulatory, anticoagulatory and profibrinolytic, or antifibrinolytic and indicative of fibrin turnover. Differences between placebo and 30 micrograms ethinyl estradiol and 2.00 mg dienogest of plasma levels of hemostatic parameters on cycle days 21 of the precycle and treatment cycle were chosen as target variables. Prothrombin fragment 1 + 2 (F 1 + 2) was chosen as the main target variable. Equivalence of F 1 + 2 between placebo and active treatment was noted. Among the procoagulatory factors, only factor VII activity was found to be increased over placebo in the active treatment group, but decreased in the placebo group. Protein C activity increased during the treatment with 30 micrograms ethinyl estradiol and 2.00 mg dienogest, and was higher than that of the placebo group in which this parameter decreased during the treatment cycle. There was a corresponding increase in fibrinolytic activity being reflected by higher plasminogen levels in the active treatment group in comparison with placebo. An increase was noted for the fibrinolytic parameter D-dimer. Apart from isolated measurements, the parameters remained in their respective normal ranges. The data combine to suggest that 30 micrograms ethinyl estradiol and 2.00 mg dienogest has a balanced effect on the hemostatic system stimulating both procoagulatory and fibrinolytic activity.

PIP: The influence on the hemostatic system of a monophasic oral contraceptive (OC) containing 30 mcg of ethinyl estradiol and 2 mg of the progestin dienogest was investigated in a double-blind, placebo-controlled study involving 40 healthy German women 19-35 years old. A total of 12 hemostatic parameters were measured on cycle days 7, 14, and 21 at baseline and during 1 treatment cycle. The prothrombin fragment 1 + 2 (an early and sensitive marker for the activation of hemostasis) was equivalent between OC users and untreated controls. Among the pre-coagulatory factors, only factor VII activity was not equivalent; on day 21, there was a decrease in the placebo group and an increase in the OC group. Also on day 21 of the treatment cycle, protein C activity increased in OC users compared to controls. There was a corresponding increase in fibrinolytic activity, reflected by higher plasminogen levels in OC users, and an increase in the fibrinolytic parameter D-dimer. In general, hemostatic parameters remained within their normal ranges. These findings confirm that the OC analyzed has a balanced effect on the hemostatic system, simultaneously stimulating both procoagulatory and fibrinolytic activity.

➤ **Modulation of ovarian function by an oral contraceptive containing 30 micrograms ethinyl estradiol in combination with 2.00 mg dienogest³.**

² Spona J, Feichtinger W, Kindermann C, Schneider B, Mellinger U, Walter F, Moore C, Gräser T. Contraception. 1997 Aug;56(2):67-75.

³ Spona J, Feichtinger W, Kindermann C, Moore C, Mellinger U, Walter F, Gräser T. Contraception. 1997 Sep;56(3):185-91.

Abstract: Twenty-two healthy female volunteers with normal ovulatory cycles, aged between 20 and 34 years (27.3 ± 4.1), were included in a single-center, noncomparative study to investigate the modulation of ovarian function by an oral contraceptive containing 30 micrograms ethinyl estradiol in combination with 2.00 mg dienogest. At baseline, during three treatment cycles and post-treatment, serum levels of luteinizing hormone, follicle-stimulating hormone, 17 beta-estradiol, and progesterone were assayed and ultrasonography was used to measure follicular size and the thickness of the endometrium. The primary efficacy variable was inhibition of ovulation as measured by ovarian activity grading. All volunteers ovulated during the pretreatment cycle. During treatment, none of the subjects had ovulatory cycles, although there was still some ovarian activity in several subjects. During the first treatment cycle, only 4% (1 subject) of cycles showed active follicle-like structures. The frequency of follicle-like structures increased to 33% and 35% during treatment cycles 2 and 3. The frequency of presumptive luteinized unruptured follicle-like structures was 5% (1 subject) and 15% (3 subjects) in treatment cycles 2 and 3. The serum hormone concentrations were effectively suppressed in comparison to baseline. The ovarian activity returned to baseline during the post-treatment period. One subject was excluded from further study because of a medical problem believed unrelated to use of the oral contraceptive. No serious adverse events were recorded during the course of the study. The results of the present investigation indicate that the modulatory effects on ovarian function of the monophasic oral-contraceptive containing 30 micrograms ethinyl estradiol combined with 2.00 mg dienogest lead to adequate suppression of ovarian activity and effective inhibition of ovulation.

- 1.2 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:

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. (...)

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 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

(...)

EXAMPLE 1

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

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 fumarate. The (...)

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

12. The method according to claim 5, wherein the progestin is dienogest. (...)

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.

Como se puede observar, esta anterioridad se revela primero que todo, la combinación entre etinil **estradiol y dienogest en formulaciones sólidas para administración oral**, específicamente en rangos de cantidad que concuerdan con los reivindicados por la solicitud colombiana en trámite, así mismo se hace mención del mismo número de unidades de dosificación que pueden tener principios activos y el número de unidades que son placebos. Entonces, puede afirmarse que la información contenida en la anterioridad afecta directamente tanto la novedad como el nivel inventivo de la solicitud colombiana en trámite, es especial de las reivindicaciones 1 a 3

- 1.3** La patente americana US 6,312,722 publicada el 06 de noviembre de 2001 y titulada "PHARMACEUTICAL COMBINED PREPARATION, KIT AND METHOD FOR HORMONAL CONTRACEPTION" revela:

(...)

ovulation. The ethinyloestradiol usually used as the oestrogen in combined preparations should increase the ovulation-inhibiting effect of the gestagen and in particular ensure stability of the cycle. In the case of administration of ethinyloestradiol alone, the daily dose that has to be used in order to inhibit ovulation is 100 μg .

Combined preparations with the most recent generation of gestagens are, for example, the monophase preparations Femovan (DE-PS 2 546 062) and Marvelon (DE-OS 2 361 120). Milvane® may be mentioned as an example of a multi-phase preparation in which the unit doses contain a gestagen of the most recent generation, namely gestodene (...)

Preferred arrangements of the present invention concern a pharmaceutical combined preparation of the type mentioned at the outset in which

- the first stage comprises 25 or 26 daily unit doses,
 - the first stage comprises a minimum of 28 and a maximum of 84 daily unit doses,
 - the first stage comprises 28 daily unit doses,
 - the first stage comprises 28 plus 7, or 28 plus a multiple of 7, daily unit doses,
 - the second stage comprises 7 daily unit doses,
 - the first stage comprises 25 or 26 daily unit doses and the second stage comprises 5 or 6 daily unit doses, so that the combined preparation has a total of 30 or 31 daily unit doses.
- (...)

Preferably, in all embodiments of the invention the oestrogen of the first hormone component is selected from the group of compounds

17 β -oestradiol,
ethynyloestradiol and
17 β -oestradiol valerate
and the gestagen is selected from the group of compounds
dienogest
gestodene,
levonorgestrel,
desogestrel,
3-ketodesogestrel,
drospironenone,
cyproterone acetate,
norgestimate and (...)

Preferably, in the present invention the oestrogen of the first hormone component is contained in each daily unit dose in a dose of

from 1.0 to 6.0 mg of 17 β -oestradiol,
from 0.015 to 0.025 mg of ethynyloestradiol,
from 1.0 to 4.0 mg of 17 β -oestradiol valerate
and the gestagen is contained in each daily unit dose in a dose of
from 1.0 to 3.0 mg of dienogest
from 0.05 to 0.075 mg of gestodene,
from 0.05 to 0.125 mg of levonorgestrel, (...)

19. Contraceptive kit according to claim 11, wherein the oestrogen of the first stage is contained in each daily unit dose in a dose of

from 1.0 to 6.0 mg of 17 β -oestradiol,
from 0.015 to 0.025 mg of ethynyloestradiol,
from 1.0 to 4.0 mg of 17 β -oestradiol valerate
and the gestagen is contained in each daily unit dose in a dose of
from 1.0 to 3.0 mg of dienogest
from 0.05 to 0.075 mg of gestodene,
from 0.05 to 0.125 mg of levonorgestrel, (...)

Esta anterioridad revela **la combinación entre etinil estradiol y dienogest en formulaciones sólidas para administración oral**, específicamente en rangos de cantidad que concuerdan con los reivindicados por la solicitud colombiana en trámite; así mismo se hace mención del mismo número de unidades de dosificación que pueden tener principios activos y el número de unidades que son placebos. En consecuencia puede afirmarse que la

información contenida en la anterioridad citada, afecta no solo la novedad sino el nivel inventivo de la solicitud colombiana en trámite.

- 1.4 La patente americana US 5,759,577 publicada el 02 de Junio de 1998 y titulada "CONTROLLED RELEASE OF STEROIDS FROM SUGAR COATINGS" revela:

A compressed medicinal tablet comprising a tablet core and a sugar coating, said sugar coating containing a dose of a hormonal steroid and a steroid release rate controlling amount of microcrystalline cellulose. (...)

In accordance with this invention, there is provided a pharmaceutical tablet comprising an internal compressed core and an external sugar coating, wherein said compressed core optionally contains no pharmacologically-active agent or one or more non-steroidal, pharmacologically-active agents that are conventionally administered in conjunction with a hormonal steroid, the improvement which comprises the incorporation of a hormonal steroid and a hormonal steroid release rate controlling amount of micro-crystalline cellulose in said sugar coating. The compressed tablet core may be devoid of any medicament or it may contain a pharmaceutical agent other than a steroid, that is compatible with the steroid and any other therapeutic agent in the sugar coating. Thus, the sugar coated tablets of this invention may contain one or more pharmacologically-active agents, where the improvement in prior sugar coated tablets comprises the incorporation of a hormonal steroid release rate controlling amount of microcrystalline cellulose in conjunction with a hormonal steroid in said sugar coating. The sugar-coated tablet may be finished with color coatings and polished as is common in coated tablets. (...)

crystalline cellulose in the sugar coating. The tablet core may have an unplasticized or plasticized seal coat designed to modify the drug release characteristics of any drug(s) contained within the core, or to protect them against moisture and/or oxygen. The non-medicated cores are those (...)

Examples of hormonal steroids suitable for incorporation into the sugar coating formulations of this invention include, for instance, one or more of the following steroids; medroxyprogesterone acetate, levonorgestrel, gestodene, medrogestone, estradiol, estriol, ethinylestradiol, mestranol, estrone, dienestrol, hexestrol, diethylstilbestrol, progesterone, desogestrel, norgestimate, hydroxyprogesterone, norethindrone, norethindone acetate, norgestrel, megestrol acetate, methyltestosterone, ethylestrenol, methandienone, oxandrolone, trimegestone, dionogest, and the like. Additionally, the tissue selective (...)

6. A pharmaceutical tablet of claim 1 in which said sugar coat contains an estrogenic steroid and a progestogenic steroid.

En esta oportunidad, la anterioridad hace mención de tabletas recubiertas de liberación controlada que contienen en combinación un esteroide estrogénico y uno esteroide progestogénico, explícitamente hace mención de Etilil estradiol y Dienogest. Más adelante menciona la intención de proteger el principio activo que queda expuesto en la cubierta de dicha formulación, lo cual coincide con el uso de ácido ascórbico (antioxidante) en la cubierta de la formulación reivindicada por la solicitud colombiana en trámite, en donde va el etinil estradiol.

En relación al empleo de ácido ascórbico, es relevante señalar que existe información de carácter científico que describe alteraciones farmacodinámicas^{4,5,6} (aumento de la concentración en sangre de etinil estradiol en presencia de ácido ascórbico debido a la competencia por la sulfatación durante el metabolismo de excreción) en la administración concomitante de etinil estradiol y de ácido ascórbico. Entonces, puede afirmarse que la información contenida en la anterioridad, afecta igualmente el nivel inventivo de la solicitud colombiana en trámite.

En conclusión, la solicitud colombiana en trámite carece tanto de novedad como de nivel inventivo, si se tiene en cuenta que en el mismo estado de la técnica ya se encuentran descritas los mismos tipos de formulaciones farmacéuticas, conteniendo la misma combinación farmacológica de dienogest y etinil estradiol, en rangos de cantidades similares de dichos principios activos; en donde dicha combinación farmacológica es ampliamente reconocida y utilizada con anterioridad en formulaciones contraceptivas.

Así las cosas, y con fundamento en los argumentos expuestos a lo largo del presente escrito, respetuosamente reitero la solicitud para que su despacho se

⁴ Back DJ, Orme ML. Pharmacokinetic drug interactions with oral contraceptives. Clin Pharmacokinet. 1990 Jun;18(6):472-84.

⁵ Back DJ, Orme ML. Pharmacokinetic drug interactions with oral contraceptives. Clin Pharmacokinet. 1990 Jun;18(6):472-84.

⁶ Weber A, Jäger R, Börner A, Klinger G, Vollanth R, Matthey K, Balogh A. Can grapefruit juice influence ethinylestradiol bioavailability? Contraception. 1996 Jan;53(1):41-7.

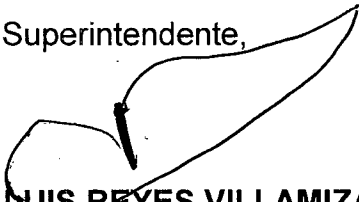
abstenga de conceder el privilegio de patente solicitado, y ordene en consecuencia el archivo del expediente respectivo.

II. PRUEBAS

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

- Abstracts de todos los artículos científicos mencionado en el acápite de FUNDAMENTOS DE LA OPOSICION.
- 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" paginas 7 a 10 y capitulo reivindicatorio.
- La patente americana US 6312722 publicada el 06 de noviembre de 2001 y titulada "PHARMACEUTICAL COMBINED PREPARATION, KIT AND METHOD FOR HORMONAL CONTRACEPCION" columnas 1 a 6 y capitulo reivindicatorio.
- La patente americana US 5759577 publicada el 02 de Junio de 1998 y titulada "CONTROLLED RELEASE OF STEROIDS FROM SUGAR COATINGS".

Señor Superintendente,



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☐ 1: Clin Pharmacokinet. 1990 Jun;18(6):472-84.

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Pharmacokinetic drug interactions with oral contraceptives.

Back DJ, Orme ML.

Department of Pharmacology and Therapeutics, University of Liverpool, England.

Oral contraceptive steroids are used by an estimated 60 to 70 million women world-wide. Over the past 20 years there have been both case reports and clinical studies on the topic of drug interactions with these agents. Some of the interactions are of definite therapeutic relevance, whereas others can be discounted as being of no clinical significance. Pharmacological interactions between oral contraceptive steroids and other compounds may be of 2 kinds: (a) drugs may impair the efficacy of oral contraceptive steroids, leading to breakthrough bleeding and pregnancy (in a few cases, the activity of the contraceptive is enhanced); (b) oral contraceptive steroids may interfere with the metabolism of other drugs. A number of anticonvulsants (phenobarbital, phenytoin, carbamazepine) are enzyme-inducing agents and thereby increase the clearance of the oral contraceptive steroids. Valproic acid has no enzyme-inducing properties, and thus women on this anticonvulsant can rely on their low dose oral contraceptive steroids for contraceptive protection. Researchers are now beginning to unravel the molecular basis of this interaction, with evidence of specific forms of cytochrome P450 (P450IIC and IIIA gene families) being induced by phenobarbital. Rifampicin, the antituberculous drug, also induces a cytochrome P450 which is a product of the P450IIIA gene subfamily. This isozyme is one of the major forms involved in 2-hydroxylation of ethinylestradiol. Broad spectrum antibiotics have been implicated in causing pill failure; case reports document the interaction, and general practitioners are convinced that it is real. The problem remains that there is still no firm clinical pharmacokinetic evidence which indicates that blood concentrations of oral contraceptive steroids are altered by antibiotics. However, perhaps this should not be a surprise, given that the incidence of the interaction may be very low. It is suggested that an individual at risk will have a low bioavailability of ethinylestradiol, a large enterohepatic recirculation and gut flora particularly susceptible to the antibiotic being used. Two drugs, ascorbic acid (vitamin C) and paracetamol (acetaminophen), give rise to increased blood concentrations of ethinylestradiol due to competition for sulphation. The interactions could have some significance to women on oral contraceptive steroids who regularly take high doses of either drug. Although on theoretical grounds adsorbents (e.g. magnesium trisilicate, aluminium hydroxide, activated charcoal and kaolin) could be expected to interfere with oral contraceptive efficacy, there is no firm evidence that this is the case. Similarly, there is no evidence that smoking alters the pharmacokinetics of oral contraceptive steroids. These agents are now well documented as being able to alter the pharmacokinetics of other concomitantly administered drugs. (ABSTRACT TRUNCATED AT 400 WORDS)

PIP: The pharmacokinetics and clinical significance of the major drug interactions seen with oral contraceptives are reviewed, both drugs interfering with pill efficacy, and situations where pills interfere with action of other drugs. Drugs affecting contraceptive efficacy include anticonvulsants, antibiotics, rifampicin, griseofulvin, ascorbic acid, and acetaminophen. Phenytoin is the most common anticonvulsant reported to cause contraceptive failure. It has been established by measurements of steady-state ethinyl estradiol levels, sex hormone binding globulin levels, and pharmacokinetic drug concentration curves that both ethinyl estradiol and levonorgestrel levels are decreased during phenytoin and carbamazepine intake. Induction of certain cytochrome P450 isozymes is probably responsible. Neither the causation or even the existence of drug interaction with antibiotics is definitely known, although case reports of pregnancies abound. Rifampicin is an exception, where enzyme induction clearly occurs. Ascorbic acid and acetaminophen are atypical for increasing the therapeutic effect of ethinyl estradiol. The effect of benzodiazepines depends on the type of drug metabolism: drugs oxidized and nitroreduced, e.g.

Related Articles

- Oral contraceptives. Are drug interactions of clinical significance? [Drug Saf. 1993]
- Drug interactions with oral contraceptive preparations. [Med J Aust. 1986]
- Drug interactions with oral contraceptives. [Drug Intell Clin Pharm. 1986]
- Clinical pharmacokinetics of contraceptive steroids. An update. [Clin Pharmacokinet. 1991]
- Drug control of steroid metabolism by the hepatic endoplasmic reticulum. [Drug Metab Rev. 1983]

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Patient Drug Information

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Phenobarbital (Luminal® Sodium) Phenobarbital, a barbiturate, is used to control epilepsy (seizures) and as a sedative to relieve anxiety. It is also used for short-term treatment of insomnia to help you fall asleep.

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1: Drug Saf. 1993 Jul;9(1):21-37.

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Oral contraceptives. Are drug interactions of clinical significance?**Shenfield GM.**

Department of Clinical Pharmacology, Royal North Shore Hospital, St Leonards, New South Wales, Australia.

There is a large quantity of literature on drug interactions with oral contraceptive (OC) steroids although their incidence is not known. The potential clinical significance of some interactions makes it important for all prescribing doctors and dentists to have some knowledge of the topic. Interactions may be divided into those in which OC effectiveness is impaired, causing breakthrough bleeding or pregnancy, those in which OC activity is enhanced by other drugs and those in which OCs interfere with the metabolism or activity of other therapeutic agents. Consideration of their pharmacology indicates that impairment of OC effect is most likely to be due to interference with ethinylestradiol. This is because this compound is sulphated in the gut wall, hydroxylated and glucuronidated in the liver, and undergoes enterohepatic recirculation. The progestogens are only metabolised in the liver and have no significant enterohepatic recirculation. Protein binding interactions are rarely of clinical importance. OC plasma concentrations may be reduced by induction of hepatic metabolism in the case of griseofulvin, rifampicin (rifampin) and several anticonvulsant drugs; valproic acid (sodium valproate) does not have this effect. Antibiotics may interfere with enterohepatic recirculation of ethinylestradiol and reduce plasma levels of active hormone. This is probably only of significance in a subgroup of women who may sometimes be suspected on history, but cannot be identified by any diagnostic test. Reasons for differences between case reports and formal studies of interactions with antibiotics are discussed. Plasma concentrations of ethinylestradiol may be increased by ascorbic acid (vitamin C) and paracetamol (acetaminophen) which compete with it for sulphation in the gut wall. Theoretically, problems may arise if these agents are stopped suddenly. Imidazole antifungal agents can inhibit ethinylestradiol metabolism and increase its plasma concentrations but the clinical significance of this is unknown. OCs have been shown to inhibit metabolism of many therapeutic drugs and increase their plasma concentrations. This may be of clinical significance in the case of benzodiazepines which are hydroxylated in the liver, but clinical effects are less certain with the other agents. OCs may induce metabolism of other drugs which are glucuronidated, including some benzodiazepines and analgesics. The clinical significance of this type of interaction is also unknown. It is suggested that all prescribers should remember to ask about OCs when taking a drug history and to consider the possibility of interactions with other drugs.

PMID: 8347289 [PubMed - indexed for MEDLINE]

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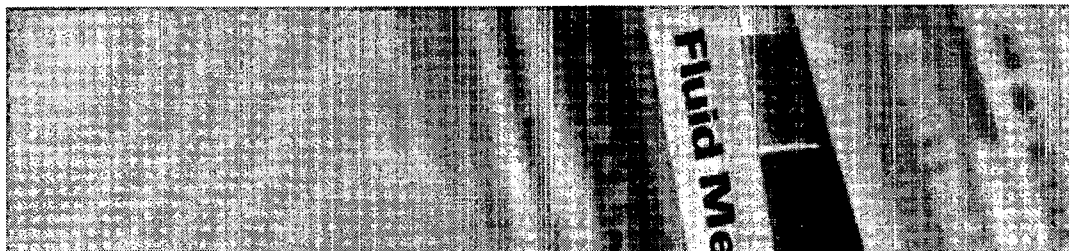
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**Titre du document / Document title**

Modulation of ovarian function by an oral contraceptive containing 30 µg ethinyl estradiol in combination with 2.00 mg dienogest

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Résumé / Abstract

Twenty-two healthy female volunteers with normal ovulatory cycles, aged between 20 and 34 years (27.3 ± 4.1), were included in a single-center, noncomparative study to investigate the modulation of ovarian function by an oral contraceptive containing 30 µg ethinyl estradiol in combination with 2.00 mg dienogest. At baseline, during three treatment cycles and post-treatment, serum levels of luteinizing hormone, follicle-stimulating hormone, 17β-estradiol, and progesterone were assayed and ultrasonography was used to measure follicular size and the thickness of the endometrium. The primary efficacy variable was inhibition of ovulation as measured by ovarian activity grading. All volunteers ovulated during the pretreatment cycle. During treatment, none of the subjects had ovulatory cycles, although there was still some ovarian activity in several subjects. During the first treatment cycle, only 4% (1 subject) of cycles showed active follicle-like structures. The frequency of follicle-like structures increased to 33% and 35% during treatment cycles 2 and 3. The frequency of presumptive luteinized unruptured follicle-like structures was 5% (1 subject) and 15% (3 subjects) in treatment cycles 2 and 3. The serum hormone concentrations were effectively suppressed in comparison to baseline. The ovarian activity returned to baseline during the post-treatment period. One subject was excluded from further study because of a medical problem believed unrelated to use of the oral contraceptive. No serious adverse events were recorded during the course of the study. The results of the present investigation indicate that the modulatory effects on ovarian function of the monophasic oral contraceptive containing 30 µg ethinyl estradiol combined with 2.00 mg dienogest lead to adequate suppression of ovarian activity and effective inhibition of ovulation.

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Ethinylestradiol ; Dienogest ; Estrogen ; Progestagen ; Estroprogestagen ; Contraceptive ; Oral administration ; Young adult ; Female ; Ovary ; Hormonal investigation ; Ovarian follicle ; Human ;

Mots-clés français / French Keywords

Ethinylestradiol ; Diénogest ; Oestrogène ; Progestatif ; Oestroprogestatif ; Contraceptif ; Voie orale ; Adulte jeune ; Femelle ; Ovaire ; Exploration hormonale ; Follicule ovarien ; Homme ;

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Ethinilestradiol ; Dienogest ; Estrógeno ; Progestágeno ; Estroprogestágeno ; Anticonceptivo ; Via oral ; Adulto joven ; Hembra ; Ovario ; Análisis hormonal ; Folículo ovárico ; Hombre ;

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Localisation / Location

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Search PubMed for [Advanced Search \(beta\)](#)[Limits](#) [Preview/Index](#) [History](#) [Clipboard](#) [Details](#)Display [AbstractPlus](#) 20 ☐ 1: Contraception. 1996 Jan;53(1):41-7.[ELSEVIER](#) [FULL-TEXT ARTICLE](#) [Links](#)**Can grapefruit juice influence ethinylestradiol bioavailability?****Weber A, Jäger R, Börner A, Klinger G, Vollan R, Matthey K, Balogh A.**

Department of Clinical Pharmacology, Friedrich Schiller University of Jena, Germany.

The effects of grapefruit juice on the bioavailability of 17 alpha-ethinylestradiol (EE2) after a single oral administration of 50 micrograms EE2 have been investigated. The pharmacokinetics of EE2 were studied in an open, randomized, cross-over study in which 13 healthy volunteers were administered the drug with herbal tea or grapefruit juice (naringin, 887 mg/ml). In contrast to herbal tea, grapefruit juice increased the peak plasma concentration (Cmax) significantly to 137% (mean; range 64% to 214%, $p = 0.0088$) and increased the area under plasma concentration-time curve from 0 to 8 hours (AUC0-8) to 128% (mean; range 81% to 180%, $p = 0.0186$). This study shows that grapefruit juice increases the bioavailable amount of EE2. A possible explanation may be that grapefruit juice inhibits the metabolic degradation of EE2. Whether the increased bioavailability of EE2 following grapefruit juice administration is of clinical importance should be investigated in long-term studies.

PMID: 8631189 [PubMed - indexed for MEDLINE]

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Interaction between grapefruit juice and midazolam in humans. [Clin Pharmacol Ther. 1995]

Grapefruit juice-felodipine interaction: effect of naringin and 6',7'-dihydroxybergamottin in humans. [Contraception. 1998]

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Search PubMed for [Advanced Search \(beta\)](#)[Limits](#) [Preview/Index](#) [History](#) [Clipboard](#) [Details](#)Display [AbstractPlus](#) 20 [All: 1](#) [Review: 0](#)☐ 1: Zentralbl Gynakol. 1997;119(12):597-606.[Links](#)**[Effect of ethinyl estradiol-dienogest combination on serum androgen concentrations]**

[Article in German]

Oettel M, Carol W, Gräser T, Klinger G, Mellinger U, Moore C, Schindler AE, Winkler UH.

Jenapharm GmbH & Co. KG, Jena.

Antiandrogens or progestins with an antiandrogenic component usually have only a weak antigonadotropic activity. It is thus possible that the antiandrogenic effect on the cellular level is cancelled or at least reduced by an increased ovarian androgen production. The aim of the four submitted clinical studies of the progestin and antiandrogen dienogest alone (0.5-2 mg/day) or of a combined regimen of ethinylestradiol (0.03 mg) plus dienogest (2 mg) (EE/DNG) was to examine the influence on the serum androgen and SHBG concentrations as well as on the serum FSH, LH, progesterone and 17 beta-estradiol concentrations in young women. Like the progesterone derivatives, dienogest has a relatively low antigonadotropic activity. Inhibition of ovulation is mainly produced by peripheral mechanisms such as the reduction of preovulatory 17 beta-estradiol secretion. Dienogest alone has no significant effects on the serum SHBG and androgen concentrations. Unlike this, the combination of EE plus DNG markedly increases SHBG concentrations (to 2.1-3.7 fold the basal levels). The decrease in serum androgens with total testosterone (by 17 and 40%), free testosterone (by 48 and 54%) and dehydroepiandrosterone sulfate (by 51%) corresponds to the values shown in the literature for other oral contraceptives with modern progestins. EE/DNG does not affect the serum concentrations of 5 alpha-dihydrotestosterone (DHT), although the marker of the peripheral transformation from T to DHT, androstenediol glucuronide, is distinctly reduced (by 38%). In a double-blind comparison no differences are found between EE/DNG and a regimen combining 0.02 mg of ethinylestradiol and 0.150 mg of desogestrel. Solely the SHBG concentrations, with EE/DNG, as expected, are significantly higher. In a sequential regimen, dienogest, chlormadinone acetate and desogestrel (progestins without binding to SHBG) enhance the inhibitory effect of ethinylestradiol sulfonate on free testosterone, whereas norethindrone acetate and levonorgestrel (progestins with a strong binding to SHBG) reduce this effect of the estrogen significantly. These results exclude the possibility that the very distinct antiandrogenic effect of dienogest on a cellular level is neutralised or reduced by an increased systemic supply of androgen.

PMID: 9483810 [PubMed - indexed for MEDLINE]

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Effect of two oral contraceptives containing ethinylestradiol and gestodene or norgestimate upon androgen parameters and serum binding proteins [Contraception. 1995]

Effect of low-dose oral contraceptives on androgenic markers and acne. [Contraception. 1999]

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(21) International Application Number: PCT/US97/12795 (22) International Filing Date: 23 July 1997 (23.07.97) (30) Priority Data: 08/686,790 26 July 1996 (26.07.96) US (71) Applicant: AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Giralda Farms, Madison, NJ 07940-0874 (US). (72) Inventor: GAST, Michael, Jay; 230 Country Lane, Phoenixville, PA 19460 (US). (74) Agents: ALICE, Ronald, W.; American Home Products Corporation, Patent Law Dept. - 2B, One Campus Drive, Parsippany, NJ 07054 (US) et al.		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: MONOPHASIC CONTRACEPTIVE METHOD AND KIT COMPRISING A COMBINATION OF A PROGESTIN AND ESTROGEN (57) Abstract This invention provides a method of contraception which comprises administering to a female of child bearing age for a combination of a progestin at a daily dosage of 40-500 μ g trimegestone, 250 μ g - 4 mg dienogest, or 250 μ g - 4 mg drospirenone, and an estrogen at a daily dosage equivalent in estrogenic activity to 10-20 μ g ethinyl estradiol for 23-25 days beginning on day 1 of the menstrual cycle, and wherein the same dosage of the progestin and estrogen combination is administered in each of the 23-25 days.		

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

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

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

DESCRIPTION OF THE INVENTION

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

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

More particularly, this invention provides a method of contraception which comprises administering to a female of child bearing age a combination of 40-500 μg 5 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 10 regimen. Alternatively, the 3-5-day interval can be pill free. The total cycle length is 28 days.

Preferred estrogens include, but are not limited to ethinyl estradiol; 17 β -estradiol; conjugated estrogens, USP; estrone or a salt thereof; and mestranol; with ethinyl estradiol being more preferred. When ethinyl estradiol is used as the estrogen, it 15 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.

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

It is preferred that the progestin/estrogen combination be administered for 24 25 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.

30

PREFERRED DAILY DOSAGES

Regimen	Trimegestone	Ethinyl Estradiol
A	250 μg	15 μg
B	125 μg	15 μg
C	75 μg	15 μg
35 D	50 μg	15 μg
E	40 μg	15 μg

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

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PREFERRED DAILY DOSAGES

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

15 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
20	D	500 µg	15 µg

25

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

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EXAMPLE 1

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

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

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WHAT IS CLAIMED IS:

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

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

- 13 -

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 μ g trimegestone, 250 μ g - 4 mg dienogest, and 250 μ g - 4 mg drospirenone, and an estrogen at a dosage equivalent in estrogenic activity to 10-20 μ g ethinyl estradiol, wherein each of the dosage units contains the same dosage of progestin and estrogen.

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

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

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

29. A contraceptive kit adapted for oral administration which comprises 28 dosage separate units, 23-25 of said dosage units each containing each containing a combination of a progestin at a dosage selected from the group consisting of 40-500 μ g trimegestone, 250 μ g - 4 mg dienogest, and 250 μ g mg drospirenone, and an estrogen at a dosage equivalent in estrogenic activity to 10-20 μ g 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.



US006312722B1

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(12) **United States Patent**
Schmidt-Gollwitzer et al.

(10) **Patent No.:** **US 6,312,722 B1**
(45) **Date of Patent:** **Nov. 6, 2001**

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

44 11 585 10/1995 (DE) .
95/07081 9/1994 (WO) .
97/01342 6/1996 (WO) .

(75) Inventors: **Karin Schmidt-Gollwitzer; Walter
Klemann**, both of Berlin (DE)

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

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(21) Appl. No.: **09/476,333**

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(57) ABSTRACT

The present invention describes a two-stage pharmaceutical combined preparation for hormonal contraception containing at least 30 daily unit doses, which preparation, in its first stage, comprises as hormonal active ingredient a combination of an oestrogen preparation and, in a dose that is at least sufficient to inhibit ovulation, a gestagen preparation, in single stage form and, in the second stage comprises as hormonal active ingredient an oestrogen preparation only, wherein the first stage comprises a minimum of 25 and a maximum of 77 daily discrete or continuous unit doses and the second stage comprises 5, 6 or 7 daily discrete or continuous unit doses, and wherein the total number of daily units is equal to the total number of days of the desired cycle of a minimum of 30 and a maximum of 84 days. This combined preparation, in the form of a monthly pack, which is used for female fertility control, permits as low as possible an oestrogen content in each individual unit dose and also has a low total hormone content per cycle of administration, with high contraceptive reliability, low incidence of follicle development, and satisfactory cycle control with reliable avoidance of intermediate bleeding as well as undesired side effects.

34 Claims, No Drawings

PHARMACEUTICAL COMBINED PREPARATION, KIT AND METHOD FOR HORMONAL CONTRACEPTION

This application is a continuation of Ser. No. 08/981,488 filed Jun. 3, 1998 now U.S. Pat. No. 6,027,749.

The present invention relates to a two-stage pharmaceutical combined preparation for hormonal contraception containing at least 30 daily unit doses, which preparation, in its first stage, comprises as hormonal active ingredient a combination of an oestrogen preparation and, in a dose that is at least sufficient to inhibit ovulation, a gestagen preparation, in single stage form and, in the second stage comprises as hormonal active ingredient an oestrogen preparation only, wherein the first stage comprises a minimum of 25 and a maximum of 77 daily discrete or continuous unit doses and the second stage comprises 5, 6 or 7 daily discrete or continuous unit doses, and wherein the total number of daily units is equal to the total number of days of the desired cycle of a minimum of 30 and a maximum of 84 days, and relates also to a corresponding pack (contraceptive kit) containing that combined preparation, and to a contraceptive method that uses the above contraceptive preparation.

Oral contraceptives in the form of combined preparations have been known since 1960 as so-called monophasic preparations. Those preparations consist of 21 unit doses that comprise active ingredient and 7 tablets or dragées that are active ingredient-free. The daily unit dose is composed of an oestrogen and gestagen. In monophasic preparations the dose of active ingredient to be administered daily is the same in each unit dose. If the dose that is to be administered daily of the active components in the individual unit doses is different in individual sections over the administration cycle, then the preparation is referred to as a so-called multi-phase preparation. Triquilar® may be mentioned as an especially well-known example (DE-AS 23 65 103).

As a result of the development of new, more active gestagens than those contained in the first oral contraceptives, a continuous reduction of the daily dose of gestagen has been possible. It has also been possible for the daily dose of oestrogen to be reduced although, as before, the oestrogen contained in hormonal contraceptives is usually ethinyloestradiol. In the development of new, improved oral contraceptives, the following three factors have been (and are) dominant:

- (1) contraceptive reliability
- (2) good cycle control, that is to say a low incidence of intermediate bleeding and
- (3) a minimum of undesired side effects should be ensured.

The contraceptive reliability is effected in particular by the gestagenic component. The daily dosage amount of that component corresponds at least to the threshold dose considered necessary for the gestagen in question to inhibit ovulation. The ethinyloestradiol usually used as the oestrogen in combined preparations should increase the ovulation-inhibiting effect of the gestagen and in particular ensure stability of the cycle. In the case of administration of ethinyloestradiol alone, the daily dose that has to be used in order to inhibit ovulation is 100 µg.

Combined preparations with the most recent generation of gestagens are, for example, the monophasic preparations Femovan (DE-PS 2 546 062) and Marvelon (DE-OS 2 361 120). Milvane® may be mentioned as an example of a multi-phase preparation in which the unit doses contain a gestagen of the most recent generation, namely gestodene (EP-0 148 724). In those three-phase preparations, usually

4–6 dragées are administered in the first phase, each dragée comprising a low dose of oestrogen and a low dose of gestagen. In the second phase of 4–6 dragées, each unit dose comprises an oestrogen in the same dose or a dose that is slightly increased (up to a maximum of twice) and a gestagen in the same dose or a dose that is slightly increased (up to a maximum of 1.5 times). In a third phase of 9–11 units, each dragée comprises an oestrogen in the same dose or a dose that is slightly reduced, at most reduced to the initial amount, and a gestagen in a dose that is further increased, to a maximum of 3 times the initial amount. 7 pill-free days then follow. Recently, multi-phase combined preparations have been proposed that may provide an extended administration of active ingredient-containing unit doses, that is to say of up to 24 days in the 28-day cycle. In those preparations the daily dose of gestagen either increases from the first, over the second, up to the third phase (EP-A 0 491 415) or decreases (EP-A 0 491 438). In order to complete the 28-day cycle, in the first case there follow 4 blind pill days, 4 placebos or 4 unit doses that contain gestagen only, and in the second case from 4 to 7 blind pill days or from 4 to 7 placebos.

The aim of the development of new oral contraceptives having a reduced daily hormone dose is to minimize the side effects described in epidemiological studies. More recent epidemiological data point towards a trend for the improved tolerability of low-dose preparations in respect of cardiovascular side effects [Thorogood M, Oral Contraceptives and Cardiovascular Disease: an Epidemiologic Overview; Pharmacoeconomics and Drug Safety, Vol. 2: 3–16 (1993); Gerstman B. B., Piper J. M., Tomita D. K., Ferguson W. J., Stadel B. V., Lundin F. E.; Oral Contraceptive Estrogen Dose and the Risk of Deep Venous Thromboembolic Disease, Am. J. E., Vol.133, No. 1, 32–36 (1991); Lidegaard O., Oral contraception and the risk of a cerebral thromboembolic attack: results of a case-control study; BMJ Vol. 306, 956–63 (1993); Vessey M., Mant D., Smith A., Yeates D., Oral contraceptives and venous thromboembolism: findings in a large prospective study; BMJ, Vol. 292 (1986); Mishell D. R., Oral Contraception: Past, Present and Future Perspectives; Int. J. Fertil., 36 Suppl., 7–18 (1991)].

A connection between the level of the daily oestrogen dose and the frequency of cardiovascular complications is accepted.

The preparation currently having the lowest dose of oestrogen is marketed as Mercilon® and contains 20 µg of ethinyloestradiol in combination with 150 µg of desogestrel in each daily unit dose over a period of 21 days with a following pill-free period of 7 days. As is to be expected, the cycle control of that preparation by comparison with preparations having a higher dose of oestrogen is somewhat poorer. A further clinically significant problem is the observation, which has been made in several studies, of a lower ovarian suppression of the preparation containing 20 µg of ethinyloestradiol. Clearly, below that very low dose of oestrogen, ripening of follicles occurs in many women, which could be detected by ultrasound examinations and hormone tests [Lunell N. O., Carlström K., Zador G., Ovulation inhibition with a combined oral contraceptive containing 20 µg ethinyloestradiol and 250 µg levonorgestrel; Acta Obstet. Gynecol. Scand. Suppl. 88: 17–21 (1979); Mall-Haefeli M., Werner-Zodrow I., Huber P. R., Klinische Erfahrungen mit Mercilon und Marvelon, unter besonderer Berücksichtigung der Ovar-Funktion (Clinical experiences with Mercilon and Marvelon with special consideration given to ovary function); Geburtsh. und Frauenheilk. 51, 35–38, Georg Thieme Verlag, Stuttgart-New York

(1991); Strobel E., Behandlung mit oralen Kontrazeptiva (Treatment with oral contraceptives); Fortschr. Med. 110 Jg. No. 20 (1992); Letter to Editor, Contraception 45: 519-521 (1992); Teichmann A. T., Brill K., Can Dose Reduction of Ethynylestradiol in OCs Jeopardize Ovarian Suppression and Cycle Control? Abstract Book, VIIIth World Congress on Human Reproduction, Bali, Indonesia (1993)].

Until recently, several days' interruption of the administration of dragées containing active ingredient was considered necessary in order to trigger withdrawal bleeding and ensure adequate cycle control.

Other preparations have been described that contain an oestrogenic and gestagenic active ingredient and that are generally administered in constant amounts in each individual unit dose over a period of 21 days, the administration of those unit doses containing an oestrogenic and gestagenic active ingredient preceding the administration of unit doses containing oestrogen only (Ijzerman, U.S. Pat. No. 3,502, 772; Pasquale, U.S. Pat. No. 4,921,843; Kuhl et al., EP-A 0499348). With those preparations, at the beginning of administration, either already on the first day of the cycle (Kuhl) or at the earliest on the second day of the cycle (Pasquale), the administration is begun of unit doses that contain an oestrogenic active ingredient only, at a dose that is below the ovulation-inhibiting dose of the oestrogenic component so that, especially in the first cycle of administration, follicle development may occur. Follicle development is considered responsible for breakthrough ovulation (Chowdry et al., "Escape" ovulation in women due to the missing of low dose combination oral contraceptive pills, Contraception, 22: 241-247, 1980; Molloy B. G. et al., "Missed pill" conception: fact or fiction? Brit. Med. J. 290, 1474-1475, 1985). The contraceptive protection is consequently placed in question. The risk of a pregnancy is therefore high especially in the case of mistakes in administration among the 20 µg ethynylestradiol preparations.

DE-OS 43 13 926 describes a pharmaceutical preparation for contraception having a minimum of four phases, which preparation consists of a fixed or sequential combination, consisting of a minimum of three phases, of ethynylestradiol or mestranol or another synthetic oestrogen, and also a gestagen, and an oestrogen preparation that is to be administered at least in the fourth phase of the cycle and that contains ethynylestradiol or mestranol and/or another synthetic and/or endogenous oestrogen. That preparation is to be administered over the entire cycle of the woman and is limited to a 28-day administration.

Common to all preparations for hormonal contraception on the market so far is that the pack unit is set to a 28-day cycle of administration (4-week rhythm). For a prevention period of one year, that is to say 12 months, administration of the contents of 13 pack units is therefore necessary.

It has, of course, already been known for a long time that the onset of menstruation, when taking an oral contraceptive where there is a continuous daily administration of both oestrogen-containing and especially gestagen-containing unit doses, can be deferred until completion of the administration of the gestagen-containing unit doses [Hamerlynck J. V. Th. H. et al., Contraception 35,3: 199-205 (1987); Luodon N. B., IPPF Med. Bull. 13,1: 2-3 (1979); Luodon N. B. et al., Brit. Med. J. 60085: 487-490 (1977/2)]. After stopping the gestagen-containing unit doses withdrawal bleeding commences. Although the ovulation-inhibiting agent according to EP-A 0 499 348 is not limited to a desired administration cycle of 28 days, the number of hormone day units containing both oestrogen and gestagen is restricted to an upper limit of 23 day units.

The aim of the present invention is to provide a combined preparation having as low as possible an oestrogen content in each individual unit dose but at the same time also a low total hormone content per cycle of administration, with which, with a high degree of contraceptive reliability, as low as possible an incidence of follicle development even in the first cycle of administration, and satisfactory cycle control with reliable prevention of intermediate bleeding, such as breakthrough bleeding and spotting, are achieved and with which undesired side effects are avoided.

This aim is achieved by the provision of the two-stage combined preparation described at the outset and also a corresponding pack containing that combined preparation (contraceptive kit) and a contraceptive method that uses the described contraceptive preparation.

Preferred arrangements of the present invention concern a pharmaceutical combined preparation of the type mentioned at the outset in which

the first stage comprises 25 or 26 daily unit doses,

the first stage comprises a minimum of 28 and a maximum of 84 daily unit doses,

the first stage comprises 28 daily unit doses,

the first stage comprises 28 plus 7, or 28 plus a multiple of 7, daily unit doses,

the second stage comprises 7 daily unit doses,

the first stage comprises 25 or 26 daily unit doses and the second stage comprises 5 or 6 daily unit doses, so that the combined preparation has a total of 30 or 31 daily unit doses.

The present invention relates furthermore to a contraceptive kit containing a minimum of 30 and a maximum of 84 daily unit doses each comprising at least one hormonal active ingredient, which kit has a first and a second stage, wherein, in its first stage, the kit comprises as hormonal active ingredient a combination of an oestrogen preparation and, in a dose at least sufficient to inhibit ovulation, a gestagen preparation, in a single stage form, and, in the second stage, comprises as hormonal active ingredient an oestrogen preparation only, the first stage comprising a minimum of 25 and a maximum of 77 daily discrete or continuous unit doses and the second stage comprising 5, 6 or 7 daily discrete or continuous unit doses, and the total number of daily units being equal to the total number of days of the desired cycle of a minimum of 30 and a maximum of 84 days.

Preferred contraceptive kits according to the present invention are characterised as follows:

the first stage comprises 25 or 26 daily unit doses,

the first stage comprises a minimum of 28 and a maximum of 84 daily unit doses,

the first stage comprises 28 daily unit doses,

the first stage comprises 28 plus 7, or 28 plus a multiple of 7, daily unit doses,

the second stage comprises 7 daily unit doses,

the first stage comprises 25 or 26 daily unit doses and the second stage comprises 5 or 6 daily unit doses, so that the kit has a total of 30 or 31 daily unit doses.

In a further embodiment of the contraceptive kit according to the invention, some of the unit doses of the first stage are arranged in periodically repeating sub-units that are separated from one another spatially and/or by other markings.

Preferably, the unit doses are arranged in sub-units at the earliest from the 26th daily unit dose, the individual sub-units can be separated from one another by perforations or

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other means suitable for separation, 7 unit doses are contained in each of the separate sub-units, the first stage comprises 28 plus 7, or 28 plus a multiple of 7, daily unit doses, and/or the second stage comprises 7 daily unit doses.

In the case of the contraceptive method according to the invention, which employs the described combined preparation, in the first stage, commencing with the first day of the cycle, a unit dose comprising an oestrogen in combination with a gestagenic component is administered daily over a minimum period of 25 and a maximum period of 77 days. There then follows the second stage in which over the remaining period of the cycle, which cycle comprises a minimum of 30 and a maximum of 84 days, an oestrogen is administered over 5, 6 or 7 days. Thus a unit dose comprising a hormonal active ingredient is administered on every day of the cycle.

With administration of the combined preparation according to the invention, recruitment of the dominant follicle, which in the spontaneous cycle occurs during the first 6 days of the menstrual cycle, is efficiently suppressed. Thus, with the combined preparation of the present invention follicle development can be suppressed and consequently breakthrough ovulations avoided, thereby increasing contraceptive reliability. This is of great importance especially where mistakes are made in administration, particularly in the case of hormonal contraceptives having a low daily dose of ethinyloestradiol. Since 25% of women who take the pill are known to make mistakes (omitting unit doses or extending the interval between the daily administration of two unit doses to more than 24 hours) (Finlay I. G., Scott M. B. G.: Patterns of contraceptive pill-taking in an inner city practice. *Br. Med. J.* 1986, 293: 601-602), the combined preparation according to the invention, when used as an ovulation-inhibiting agent, increases contraceptive reliability. This is true in particular in the case of the lowest-dose preparations.

In particular, however, this higher number of daily unit doses comprising both oestrogen and gestagen results in an extension of the cycle and a reduced frequency of withdrawal bleeding.

The subsequent stage, in which unit doses that comprise as hormonal active ingredient an oestrogenic component only are administered daily over 5, 6 or 7 days, ensures a withdrawal bleeding and causes a stimulation of progesterone receptors in the endometrium, as a result of which a reduced rate of intermediate bleeding compared with conventional low-dose preparations is achieved in the subsequent administration cycle.

In conjunction with the extended phase of administration of oestrogen- and gestagen-containing unit doses, for example an extension of the menstrual cycles to 30 or 31 days (monthly pack) is thus possible.

According to the preferred variants an optional postponement of the withdrawal bleeding up to day 77 is possible, the bleeding commencing after the unit doses comprising oestrogen and gestagen have been stopped.

A variable manipulation of the initiation of the withdrawal bleeding is possible with the contraceptive kit according to the present invention, in which the unit doses of the first stage, at the earliest from the 26th daily unit dose, are arranged in sub-units that can be separated from one another by perforations or some other suitable means of separation.

The contraceptive kit according to the invention is constructed, for example, in the form of a blister in which each individual segment, each of which preferably contains 7 unit doses of the first stage, can conveniently and easily be separated by means of perforations made in the base plate of the blister.

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It is, however, also possible for the sub-units each to be in the form of individual separate blisters or for the, for example, 28 unit doses of the first stage to be in a first blister and for the following unit doses of the first stage to be in a second blister in which sub-units can be separated from one another by perforations in the described manner.

Preferably, in all embodiments of the invention the oestrogen of the first hormone component is selected from the group of compounds

17 β -oestradiol,
ethinyloestradiol and
17 β -oestradiol valerate

and the gestagen is selected from the group of compounds

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

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

17 β -oestradiol,
ethinyloestradiol and
17 β -oestradiol valerate.

Preferably, in the present invention the oestrogen of the first hormone component is contained in each daily unit dose in a dose of

from 1.0 to 6.0 mg of 17 β -oestradiol,
from 0.015 to 0.025 mg of ethinyloestradiol,
from 1.0 to 4.0 mg of 17 β -oestradiol valerate

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

from 1.0 to 3.0 mg of dienogest
from 0.05 to 0.075 mg of gestodene,
from 0.05 to 0.125 mg of levonorgestrel,
from 0.06 to 0.15 mg of desogestrel,
from 0.06 to 0.15 mg of 3-ketodesogestrel,
from 1.0 to 3.0 mg of drospironone,
from 1.0 to 2.0 mg of cyproterone acetate,
from 0.2 mg to 0.3 mg of norgestimate
from 0.35 to 0.75 mg of norethisterone.

The second hormone component comprises the oestrogen in each daily unit dose preferably in an amount of

from 1.0 to 6.0 mg of 17 β -oestradiol,
from 0.002 to 0.04 mg of ethinyloestradiol,
from 1.0 to 4.0 mg of 17 β -oestradiol valerate.

According to an especially preferred embodiment the second hormone component contains as oestrogen ethinyloestradiol in an amount of from 0.01 to 0.015 mg in each daily unit dose.

There come into consideration as oestrogen for the first and for the second hormone component especially ethinyloestradiol or the natural oestradiol.

Of the gestagens mentioned for the second hormone component attention is drawn to gestodene; levonorgestrel is also preferred.

17 β -oestradiol valerate, which may be contained as the oestrogen both in the first and in the second hormone

second hormone component, which contains exclusively an oestrogen (E), for a total of a minimum of 30 and a maximum of 84 days in the administration cycle. In the second (next) menstrual cycle, administration of the first unit dose of the first hormone component of a new pack unit (kit) of the pharmaceutical combined preparation according to the invention is commenced on day one of that cycle, without any pause in administration.

With that combined preparation, pronounced ovarian suppression without frequent follicle ripening, and also excellent cycle control, can be achieved with a low daily oestrogen dose, a low total amount of oestrogen and a low total amount of hormone per administration cycle.

The advantages of that combined preparation according to the invention (ovulation-inhibiting agent) administered over a minimum of 30 and a maximum of 84 days per cycle compared with the preparations described hitherto, especially those having a daily ethinylestradiol dose of less than 30 µg and those with a pill-free period, may be characterised as follows:

1. A significantly lower frequency of follicle development in the user. This means a lower risk of breakthrough ovulation and consequently a greater contraceptive reliability especially where mistakes are made in administration.
2. The recruitment of the dominant follicle is effectively suppressed by the extension of the administration of the combination.
3. The administration of 5, 6 or 7 daily oestrogen unit doses following the administration of the combination dose of the first stage results in a clearly improved cycle control and in a lower incidence of side effects, such as headaches within the framework of premenstrual syndrome.
4. Other clinical symptoms that are attributable to strongly fluctuating endogenous levels of oestrogen, such as, for example, tenderness of the breasts, are likewise distinctly reduced on account of the significantly stronger ovarian suppression.
5. As a result of the freedom from bleeding (amenorrhoea) for a longer period, there is an increased acceptance by the user; this is true especially as the number of unit doses in the first stage increases.
6. The negative effects that occur with or as a result of bleeding, such as, for example, anaemia, cramp, queasiness etc. occur less frequently.
7. Constant low oestrogen and gestagen levels; consequent avoidance of metabolic variations and as a result improvement of tolerability.
8. A possible pregnancy as a result of mistakes in administration is recognisable by the absence of withdrawal bleeding after stopping the oestrogen- and gestagen-containing unit doses.

The formulation of an oestrogen and gestagen for the preparation of a combined preparation according to the invention is effected in a manner completely analogous to that already known for conventional oral contraceptives having a 21-day administration period of active ingredients, such as, for example, Femovan® (ethinylestradiol/gestodene) or Microgynon® (ethinylestradiol/levonorgestrel). The formulation of the exclusively oestrogen-containing unit doses can also be carried out in a completely analogous manner to that known for oestrogen-containing agents designed for oral administration that are already available, for example Progynon®. The unit doses

of the first stage of the preparation according to the invention may also be in the form of a plaster (transdermal application), an implant or another depot formulation and thus administered continuously.

As a form of packing for the combined preparation according to the invention, a blister pack constructed in the manner according to the invention is generally used; other forms of packing known for that purpose are, however, also possible.

In order to determine equivalently effective amounts of ethinylestradiol and 17β-oestradiol on the one hand and of different gestagens, such as gestodene, levonorgestrel, desogestrel and 3-ketodesogestrel, on the other hand, reference is made to the data given in EP-A-0 253 607. Further details for determining dosage equivalents of different gestagenic active ingredients may be found, for example, in "Probleme der Dosisfindung: Sexualhormone" (Problems of dosage determination: sexual hormones); F. Neumann et al. in "Arzneimittelforschung" (Drug Research) 27, 2a, 296-318 (1977) and in "Aktuelle Entwicklungen in der hormonal Kontrazeption" (Current developments in hormonal contraception), H. Kuhl in "Gynäkologie" 25: 231-240 (1992).

What is claimed is:

1. Two-stage pharmaceutical combined preparation for hormonal contraception containing at least 30 daily unit doses, which preparation, in its first stage, comprises as hormonal active ingredient a combination of an oestrogen preparation and, in a dose that is sufficient to inhibit ovulation, a gestagen preparation, in single stage form and, in the second stage comprises as the only hormonal active ingredient an ethinylestradiol in an amount from 0.01 to 0.015 mg in each daily unit dose, wherein the first stage comprises a minimum of 25 and a maximum of 77 daily discrete or continuous unit doses and the second stage comprises 5, 6 or 7 daily discrete or continuous unit doses, and wherein the total number of daily units is equal to the total number of days of the desired cycle of a minimum of 30 and a maximum of 84 days.
2. Combined preparation according to claim 1, wherein the first stage comprises 25 or 26 daily unit doses.
3. Combined preparation according to claim 1, wherein the first stage comprises a minimum of 28 and a maximum of 77 daily unit doses.
4. Combined preparation according to claim 3, wherein the first stage comprises 28 daily unit doses.
5. Combined preparation according to claim 3, wherein the first stage comprises 28 plus 7, or 28 plus a multiple of 7, daily unit doses.
6. Combined preparation according to claim 1, wherein the second stage comprises 7 daily unit doses.
7. Combined preparation according to claim 2, wherein the second stage comprises 5 or 6 daily unit doses, so that the combined preparation has a total of 30 or 31 daily unit doses.
8. Two-stage pharmaceutical combined preparation for hormonal contraception containing at least 30 daily unit doses, which preparation, in its first stage, comprises as hormonal active ingredient a combination of an oestrogen preparation and, in a dose that is at least sufficient to inhibit ovulation, a gestagen preparation, in single stage form and, in the second stage comprises as hormonal active ingredient an oestrogen preparation only in an amount which is effective to produce withdrawal bleeding and stimulate progesterone receptors in the endometrium, wherein the first stage comprises a minimum of 25 doses and the second stage comprises 5, 6 or 7 daily discrete or continuous unit doses,

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and wherein the total number of daily units is equal to the total number of days of the desired cycle of a minimum of 30 and a maximum of 84 days.

9. Combined preparation according to claim 1, wherein the oestrogen of the first stage is contained in each daily unit dose in a dose of

- from 1.0 to 6.0 mg of 17 β -oestradiol,
- from 0.015 to 0.025 mg of ethynyloestradiol,
- from 1.0 to 4.0 mg of 17 β -oestradiol valerate

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

- from 1.0 to 3.0 mg of dienogest
- from 0.05 to 0.075 mg of gestodene,
- from 0.05 to 0.125 mg of levonorgestrel,
- from 0.06 to 0.15 mg of desogestrel,
- from 0.06 to 0.15 mg of 3-ketodesogestrel,
- from 1.0 to 3.0 mg of drospironenone,
- from 1.0 to 2.0 mg of cyproterone acetate,
- from 0.2 mg to 0.3 mg of norgestimate
- from 0.35 to 0.75 mg of norethisterone.

10. Two-stage pharmaceutical combined preparation according to claim 8, wherein the second stage hormonal active ingredient is ethynyloestradiol in an amount from 0.01 to 0.015 mg in each daily unit dose.

11. Contraceptive kit containing at least 30 daily unit doses each containing at least one hormonal active ingredient, having a first and a second stage, which kit, in its first stage, comprises as hormonal active ingredient a combination of an oestrogen preparation and, in a dose that is sufficient to inhibit ovulation, a gestagen preparation, in single stage form and, in the second stage comprises as the only hormonal active ingredient an ethynyloestradiol in an amount from 0.01 to 0.015 mg in each daily unit dose, wherein the first stage comprises a minimum of 25 and a maximum of 77 daily discrete or continuous unit doses and the second stage comprises 5, 6 or 7 daily discrete or continuous unit doses, and wherein the total number of daily units is equal to the total number of days of the desired cycle of a minimum of 30 and a maximum of 84 days.

12. Contraceptive kit according to claim 11, wherein the first stage comprises 25 or 26 daily unit doses.

13. Contraceptive kit according to claim 11, wherein the first stage comprises a minimum of 28 and a maximum of 84 daily unit doses.

14. Contraceptive kit according to claim 13, wherein the first stage comprises 28 daily unit doses.

15. Contraceptive kit according to claim 13, wherein the first stage comprises 28 plus 7, or 28 plus a multiple of 7, daily unit doses.

16. Contraceptive kit according to claim 11, wherein the second stage comprises 7 daily unit doses.

17. Contraceptive kit according to claim 12, wherein the second stage comprises 5 or 6 daily unit doses, so that the kit has a total of 30 or 31 daily unit doses.

18. Method of contraception in female mammals comprising a sequential administration for a minimum of 30 and a maximum of 84 days of daily unit doses of a minimum of 25 and a maximum of 77 daily discrete or continuous unit doses during a first stage and 5, 6 or 7 daily discrete or continuous unit doses during a second stage, comprising as hormonal active ingredient in the first stage a combination of an oestrogen preparation and, in a dose that is sufficient to inhibit ovulation, a gestagen preparation, in single stage form, and comprising as the only hormonal active ingredient in the second stage an ethynyloestradiol in an amount from 0.01 to 0.015 mg in each daily unit dose.

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19. Contraceptive kit according to claim 11, wherein the oestrogen of the first stage is contained in each daily unit dose in a dose of

- from 1.0 to 6.0 mg of 17 β -oestradiol,
- from 0.015 to 0.025 mg of ethynyloestradiol,
- from 1.0 to 4.0 mg of 17 β -oestradiol valerate

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

- from 1.0 to 3.0 mg of dienogest
- from 0.05 to 0.075 mg of gestodene,
- from 0.05 to 0.125 mg of levonorgestrel,
- from 0.06 to 0.15 mg of desogestrel,
- from 0.06 to 0.15 mg of 3-ketodesogestrel,
- from 1.0 to 3.0 mg of drospironenone,
- from 1.0 to 2.0 mg of cyproterone acetate,
- from 0.2 mg to 0.3 mg of norgestimate
- from 0.35 to 0.75 mg of norethisterone.

20. Method according to claim 18 wherein the first stage 25 or 26 daily unit doses are administered.

21. Contraceptive kit containing at least 30 daily unit doses each containing at least one hormonal active ingredient, having a first and a second stage, which kit, in its first stage, comprises as hormonal active ingredient a combination of an oestrogen preparation and, in a dose that is sufficient to inhibit ovulation, a gestagen preparation, in single stage form and, in its second stage comprises as the only hormonal active ingredient an ethynyloestradiol in an amount from 0.01 to 0.015 mg in each daily unit dose, wherein the first stage comprises a minimum of 25 and a maximum of 77 daily discrete or continuous unit doses and second stage comprises 5, 6 or 7 daily discrete or continuous unit doses, and wherein the total number of daily units is equal to the total number of days of the desired cycle of a minimum of 30 and a maximum of 84 days, some of the unit doses of the first stage being arranged in periodically repeating sub-units that are separated from one another spatially and/or by other markings.

22. Contraceptive kit according to claim 21, wherein the unit doses are arranged in sub-units at the earliest from the 26th daily unit dose.

23. Contraceptive kit according to claim 21 wherein the individual sub-units can be separated from one another by perforations or other means suitable for separation.

24. Contraceptive kit according to claim 21, wherein the separate sub-units each contain 7 unit doses.

25. Contraceptive kit according to claim 21 wherein, the first stage comprises 28 plus 7, or 28 plus a multiple of 7, daily unit doses.

26. Contraceptive kit according to claim 21 wherein, the second stage comprises 7 daily unit doses.

27. Method according to claim 18, wherein the first stage a minimum of 28 and a maximum of 77 daily unit doses are administered.

28. Contraceptive kit according to claim 21, wherein the oestrogen of the first stage is contained in each daily unit dose in a dose of

- from 1.0 to 6.0 mg of 17 β -oestradiol,
- from 0.015 to 0.025 mg of ethynyloestradiol,
- from 1.0 to 4.0 mg of 17 β -oestradiol valerate

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

- from 1.0 to 3.0 mg of dienogest
- from 0.05 to 0.075 mg of gestodene,
- from 0.05 to 0.125 mg of levonorgestrel,

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from 0.06 to 0.15 mg of desogestrel,
from 0.06 to 0.15 mg of 3-ketodesogestrel,
from 1.0 to 3.0 mg of drospironone,
from 1.0 to 2.0 mg of cyproterone acetate,
from 0.2 mg to 0.3 mg of norgestimate
from 0.35 to 0.75 mg of norethisterone.

29. Method according to claim 27, wherein in the first stage 28 daily unit doses are administered.

30. Method according to claim 27, wherein in the first stage 28 plus 7, or 28 plus a multiple of 7, daily unit doses are administered.

31. Method according to claim 18, wherein in the second stage 7 daily unit doses are administered.

32. Method according to claim 20, wherein in the second stage 5 or 6 daily unit doses are administered.

33. Method according to claim 18 wherein the oestrogen of the first stage is administered in each daily unit dose in a dose of

from 1.0 to 6.0 mg of 17 β -oestradiol,

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from 0.015 to 0.025 mg of ethynyloestradiol,
from 1.0 to 4.0 mg of 17 β -oestradiol valerate
and the gestagen is administered in each daily unit dose in a dose of

from 1.0 to 3.0 mg of dienogest

from 0.05 to 0.075 mg of gestodene,

from 0.05 to 0.125 mg of levonorgestrel,

from 0.06 to 0.15 mg of desogestrel,

from 0.06 to 0.15 mg of 3-ketodesogestrel,

from 1.0 to 3.0 mg of drospironone,

from 1.0 to 2.0 mg of cyproterone acetate,

from 0.2 mg to 0.3 mg of norgestimate

from 0.35 to 0.75 mg of norethisterone.

34. Method according to claim 18 in which the female mammal is a homo sapiens.

* * * * *



US005759577A

United States Patent [19]
Barcomb

[11] **Patent Number:** 5,759,577
 [45] **Date of Patent:** Jun. 2, 1998

[54] **CONTROLLED RELEASE OF STEROIDS
 FROM SUGAR COATINGS**

[75] **Inventor:** Reginald J. Barcomb, Mooers Forks,
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[73] **Assignee:** American Home Products
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[21] **Appl. No.:** 637,139

[22] **Filed:** Apr. 24, 1996

Related U.S. Application Data

[63] **Continuation-in-part of Ser. No. 373,667, Jan. 17, 1995, Pat.
 No. 5,547,948.**

[51] **Int. Cl.⁶** A61K 9/36; A61K 31/56;
 A61K 31/565; A61K 31/57

[52] **U.S. Cl.** 424/479; 514/170; 514/171;
 514/843; 514/899

[58] **Field of Search** 424/479; 514/170.
 514/171, 843, 899

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Primary Examiner—Shep K. Rose
Attorney, Agent, or Firm—Steven R. Eck

[57] **ABSTRACT**

A compressed medicinal tablet comprising a tablet core and
 a sugar coating, said sugar coating containing a dose of a
 hormonal steroid and a steroid release rate controlling
 amount of microcrystalline cellulose.

6 Claims, No Drawings

CONTROLLED RELEASE OF STEROIDS FROM SUGAR COATINGS

RELATED APPLICATIONS

This application is a continuation-in-part of co-pending application Ser. No. 08/373,667, filed Jan. 17, 1995, by Reginald J. Barcomb, now U.S. Pat. No. 5,547,948.

BACKGROUND OF THE INVENTION

In the past three decades, substantial effort has gone into the identification of methods for controlling the rate of release of drug from pharmaceutical tablets. Excipients have been incorporated into tablet cores to control dissolution, and hence absorption, of drugs. Tablets and spheroids have been coated with polymers to provide slow, diffusion-controlled release or site-specific release of drugs.

Tablets and encapsulated spheroid dosage forms have also been prepared containing multiple drugs, either in admixture or as separate tablet layers or spheroids. The drugs are provided to perform multiple functions or to provide synergism. Such tablets are especially useful in those circumstances where conventional therapy dictates the use of more than one drug possessing different but compatible activities. For example, diuretic agents are frequently administered with antihypertensive agents, and progestational agents in conjunction with estrogens.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with this invention, there is provided a pharmaceutical tablet comprising an internal compressed core and an external sugar coating, wherein said compressed core optionally contains no pharmacologically-active agent or one or more non-steroidal, pharmacologically-active agents that are conventionally administered in conjunction with a hormonal steroid, the improvement which comprises the incorporation of a hormonal steroid and a hormonal steroid release rate controlling amount of micro-crystalline cellulose in said sugar coating. The compressed tablet core may be devoid of any medicament or it may contain a pharmaceutical agent other than a steroid, that is compatible with the steroid and any other therapeutic agent in the sugar coating. Thus, the sugar coated tablets of this invention may contain one or more pharmacologically-active agents, where the improvement in prior sugar coated tablets comprises the incorporation of a hormonal steroid release rate controlling amount of microcrystalline cellulose in conjunction with a hormonal steroid in said sugar coating. The sugar-coated tablet may be finished with color coatings and polished as is common in coated tablets.

The contents of the tablet core are quite independent from the sugar coating in the sense that the sugar coating and the hormonal steroid contained in it are dissolved before disintegration of the compressed tablet core and dissolution of any drug component present in the core. The excipient components employed in formulation of the core tablet may include pharmaceutically-acceptable water-soluble and/or insoluble substances such as lactose, calcium phosphate, starch, calcium carbonate, dextrose, sorbitol, mannitol, microcrystalline cellulose, sucrose, polyvinylpyrrolidone, methylcellulose, carboxymethylcellulose, alginates, hydroxypropylcellulose, hydroxypropylmethyl-cellulose, ethylcellulose, croscarmellose sodium, sodium starch glycolate, magnesium stearate, stearic acid, polyethylene glycol, sodium lauryl sulfate, fumed silica, talc and the like.

The sugar coat containing the hormonal steroid also contains a steroid release rate-controlling amount of micro-

crystalline cellulose and, in certain circumstances, polyvinylpyrrolidone to aid in application of the sugar coat.

The tablet core is produced by compression of an admixture, which has preferably been granulated, of the pharmaceutically-acceptable excipients, and, if desired, a therapeutic agent compatible with the steroid to be incorporated with the release rate controlling amount of microcrystalline cellulose in the sugar coating. The tablet core may have an unplasticized or plasticized seal coat designed to modify the drug release characteristics of any drug(s) contained within the core, or to protect them against moisture and/or oxygen. The non-medicated cores are those conventionally employed as placebo tablets in pharmacological studies.

DETAILED DESCRIPTION OF THE INVENTION

This invention provides an improved compressed tablet in which, in addition to a conventional internal tablet core optionally containing no drug or one or more drugs that are pharmacologically compatible with a steroid in the external sugar coating, a sugar coating is present which comprises a hormonal steroid in an amount of about 0.1 to about 20 percent by weight of the sugar coating; microcrystalline cellulose in an amount from about 0.1 to about 3 percent by weight of the sugar coating; polyvinylpyrrolidone in from about 0 to about 5 percent by weight of the sugar coating; and sugar. On a unit dose basis, the tablet contains about 0.01 to about 50 milligrams, preferably about 0.015 to about 40 milligrams and more preferably about 0.02 to 30 milligrams, of total hormonal steroid load in the loaded sugar coating layer. If desired, an undercoat of inert filled sugar may be applied over a seal coat prior to the steroid loaded sugar coat layer. The inert filler-containing sub-layer sugar coating may be made up with sucrose containing about 7.5 to about 15 percent microcrystalline cellulose. The outer sugar coating may contain a coloring agent such as titanium dioxide or a primary, secondary or grayed tint as is customary in the tableting art. If desired, the coloring agent may be applied as a separate coating layer over the outer sugar layer. A final polish may be used to further finish and complete the tablet.

The sugar used in production of the sugar coatings referred to throughout this specification is a sugar product, such as sucrose, derived from beet or cane sources or starch, saccharide or polysaccharide converted sources, which are considered suitable for tablet coating purposes. The currently preferred sugar is sucrose.

It has been discovered that the release of a hormonal steroid from the sugar coating can be controlled by limiting the quantity of microcrystalline cellulose to from about 0.1 to about 3 percent by weight of the sugar coating. This use of a small quantity of microcrystalline cellulose in the sugar coat is unlike the use of this excipient as a compression aid or to assist disintegration of a tablet core. In the latter case, the concentration of microcrystalline cellulose may rise to as high as 15 to 30 percent of weight.

Examples of hormonal steroids suitable for incorporation into the sugar coating formulations of this invention include, for instance, one or more of the following steroids; medroxyprogesterone acetate, levonorgestrel, gestodene, medrogestone, estradiol, estriol, ethinylestradiol, mestranol, estrone, dienestrol, hexestrol, diethylstilbestrol, progesterone, desogestrel, norgestimate, hydroxyprogesterone, norethindrone, norethindrone acetate, norgestrel, megesterol acetate, methyltestosterone,

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ethylestrenol, methandienone, oxandrolone, trimegestone, dionogest, and the like. Additionally, the tissue selective progestones and/or progesterone antagonists which may or may not have the typical steroidal functionality may be formulated into this technology. These include, but are not limited to: RU-486, onapristone, ZK-137316, ORG-31730, and HRP-2000. Where desired, estrogenic steroids and progestogenic steroids may be used in combination in the sugar coatings.

To illustrate in vitro dissolution rate control of steroid in the absence and presence of microcrystalline cellulose, the following illustrative examples are presented, without limitation:

EXAMPLE 1

A sugar coating consisting of the following solids was applied over a tablet core using either a non-perforated or perforated coating pan:

Sucrose, NF	87%
Polyvinylpyrrolidone	3%
Medroxyprogesterone Acetate, USP	10%

The rate of dissolution of the steroid was determined in accordance with <711> of USP XX, p.959 (1980), employing Apparatus 2, operating at 50 rpm by dissolving in 0.54% sodium lauryl sulfate in water at 37° C. in six repeated trials (Method A). CV represents the coefficient of variation between these trials expressed as a percentage.

Time (min.)	Percent Steroid Released (CV %)
5	93 (5.2)
10	94 (5.3)
30	95 (5.3)
60	95 (5.4)
120	95 (5.4)

EXAMPLE 2

Tablets coated in the same manner with the same sugar coating as above were dissolved in 0.13% sodium lauryl sulfate in 0.1N HCl at 37° C. using USP Apparatus 1 at 100 rpm, in six trials (method B). The results of this study were:

Time (min.)	Percent Steroid Released (CV %)
5	83 (6.0)
10	85 (5.8)
30	85 (6.2)
60	85 (6.1)
120	85 (6.2)

EXAMPLE 3

Additional tablets coated in the same manner with the same sugar composition were subjected to a flow-through dissolution test procedure in 0.12% sodium lauryl sulfate in 0.1N HCl at 37° C. using a SOTAX Dissotest Apparatus at 5.7 mL/min. flow rate (Method C). The results of three separate runs were as follows:

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Time (min.)	Percent Steroid Released (CV %)
30	90.9 (2.9)
60	94.2 (3.0)
90	95.3 (2.9)
120	96.0 (3.0)
210	97.4 (3.0)
300	98.9 (3.6)

From these in vitro studies it is clear that medroxyprogesterone acetate, used here as a typical steroid, is released from the sugar coating extremely rapidly.

EXAMPLE 4

For comparison purposes, and to illustrate the unexpected properties of the sugar coatings of this invention, a sugar coating consisting of the following solids was applied over a tablet core:

Sucrose, NF	86.5%
Microcrystalline Cellulose	0.5%
PVP	3.0%
Medroxyprogesterone Acetate, USP	10.0%

Employing the microcrystalline cellulose—containing sugar coated tablets and following Method A, the following in vitro dissolution data were obtained from three runs:

Time (min.)	Percent Steroid Released (CV %)
5	19.5 (49.5)
10	29.9 (32.8)
30	50.0 (23.0)
60	61.6 (19.5)
120	74.2 (19.2)

EXAMPLE 5

With additional microcrystalline cellulose—containing sugar coated tablets prepared in the same manner as above, following Method B in six runs, the following data were obtained:

Time (min.)	Percent Steroid Released (CV %)
5	2.3 (34.4)
10	8.2 (27.0)
30	17.9 (16.1)
60	26.5 (13.6)
120	32.7 (16.6)

EXAMPLE 6

And, following method C, with the tablets containing microcrystalline cellulose in the sugar coating, in three runs, the following data were obtained:

Time (min.)	Percent Steroid Released (CV %)
30	2.8 (34.4)
60	4.1 (24.8)
90	5.1 (22.3)
120	6.4 (22.3)

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-continued

Time (min.)	Percent Steroid Released (CV %)
210	11.0 (19.4)
300	14.3 (11.0)

From these data it is apparent that a small amount of microcrystalline cellulose in the sugar coating (in this case 0.5% by weight of the sugar coating solids) has markedly retard the release rate of hormonal steroid.

EXAMPLE 7

Sugar coated tablets were prepared in which the sugar coat contained 0.0%, 0.5% or 2% microcrystalline cellulose in combination with 3.0% polyvinyl pyrrolidone, 10.0% medroxyprogesterone acetate and sucrose. These tablets were fed to four beagle dogs under fasting conditions and the blood plasma levels of steroid were determined at 0, 0.5, 1, 1.5, 2, 3, 5, 8, 12, 16, and 24 hours. The resulting data were plotted, the area under the curve (AUC) calculated for a twenty four hour period and the time at which the maximum plasma concentration occurred was determined to be as follows:

Microcrystalline Cellulose %	AUC(0-24 Hrs) ngxlr/mL	tmax (Hr)	Cmax (ng/mL)
0.0	345	0.6	37.8
0.5	294	1.0	36.9
2.0	294	1.1	24.6

From these in vivo dog data, it is obvious that a marked change in bioavailability of a hormonal steroid occurs as the concentration of microcrystalline cellulose in the sugar coating increases from 0.0 to one containing 0.5 to 2.0% microcrystalline cellulose. Thus, the rate of release of hormonal steroid incorporated in a sugar coating may be controlled by incorporation of very small amounts of microcrystalline cellulose into sugar coating.

EXAMPLE 8

Sugar coated tablets were prepared in which the sugar coat contained 0.25%, 0.5% or 0.8% microcrystalline cellulose in combination with 0.5% polyvinyl pyrrolidone, 5.0% medroxyprogesterone acetate and sucrose. These tablets were subjected to an in vitro dissolution test employing the USP Disintegration Apparatus (USP XX, <201>, p958) (1980) with a 0.54% sodium lauryl sulfate dissolution medium at 37° C. The following test data were obtained:

Percentage Medroxyprogesterone Acetate Dissolved (CV %)			
Time (Minutes)	0.25% Microcrystalline Cellulose	0.5% Microcrystalline Cellulose	0.8% Microcrystalline Cellulose
15	97.8 (5.2)	72.6 (9.5)	32.4 (15.2)
30	98.8 (5.3)	89.9 (6.3)	62.8 (8.2)
45	99.3 (5.2)	95.2 (5.6)	76.6 (6.9)
60	99.1 (5.2)	98.3 (5.7)	84.8 (6.6)
90	99.9 (5.3)	100.9 (6.0)	94.4 (6.5)
120	100.3 (5.6)	102.4 (5.3)	98.0 (7.1)

These dosage forms were also evaluated in a human bioavailability study. The dosage forms were administered in a cross-over design to twelve healthy female subjects.

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Blood samples were collected at 0.5, 1, 1.5, 2, 2.5, 3, 4.5, 6, 8, and 12 hours and the plasma assayed for medroxyprogesterone acetate. The following data were obtained:

Microcrystalline Cellulose	AUC (0-12 h)	tmax (hr)	Cmax (ng/mL)
0.25%	26.0 ± 14.3*	2.9 ± 1.3	4.24 ± 3.0
0.5%	25.8 ± 10.5	3.2 ± 1.2	3.88 ± 1.87
0.8%	13.2 ± 4.0	3.9 ± 1.6	1.99 ± 0.73

*Mean values ± 1 Standard Deviation

From the in vitro dissolution and in vivo human bioavailability data, it is clear that the drug release characteristics and bioavailability of the hormonal steroid, are controlled by the concentration of microcrystalline cellulose in the sugar coating.

EXAMPLE 9

A sugar coating containing 5 mg of medrogestone in a matrix of sucrose with 0.4% microcrystalline cellulose and 0.5% polyvinyl pyrrolidone was applied to a sealed and sugar-coated tablet core. The in vitro dissolution profile of this dosage form was compared to that of a rapidly-disintegrating compressed tablet containing 5 mg of medrogestone using the dissolution test described in <711> of USP XX, p. 959 (1980) employing Apparatus 2 operating at 50 r.p.m. with 900 mL of 0.54% sodium lauryl sulfate at 37° C. The following data were obtained:

Mean Percentage Medrogestone Released (CV %)		
Time (Minutes)	Conventional Rapidly Disintegrating Tablet	Sugar Coated Tablet Containing Medrogestone in Sugar Coat
15	95 (2.0)	6 (11.2)
30	95 (2.9)	11 (6.9)
45	97 (1.6)	15 (6.4)
60	97 (1.9)	18 (6.6)
120	98 (1.9)	25 (6.2)

The dramatic effect of reduced dissolution of medrogestone when the hormone is incorporated in a sugar coat containing 0.4% microcrystalline cellulose is clearly demonstrated.

One preferred embodiment of this invention is a compressed tablet in which the tablet core contains a unit dose of an estrogenic compound or a mixture thereof in an amount of from about 0.1 to about 5.0 milligrams, or more preferably from about 0.3 to about 2.5 milligrams, in combination with standard excipient compression aids and fillers. Most desirably, the conjugated estrogens found in the tablet core comprise the naturally occurring conjugated estrogen product known as Premarin®. Over a sugar coat on the compressed tablet is applied an additional sugar coat containing about 1 to about 50 milligrams, and preferably about 1.5 to about 30 milligrams, of medroxyprogesterone acetate, a color coat, and finally, a polish coat. In other applications, it is preferable to employ a non-medicated core with a sugar coating containing a steroid such as trimegestone and more preferably, a sugar coating containing a mixture of steroids such as trimegestone and a conjugated estrogen.

What is claimed is:

1. In a pharmaceutical tablet comprising an internal compressed core and an external sugar coating, wherein said

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compressed core optionally contains no pharmacologically-active agent or one or more non-steroidal, pharmacologically-active agents that are conventionally administered in conjunction with a hormonal steroid, the improvement which comprises the incorporation of a hormonal steroid and a hormonal steroid release rate controlling amount of micro-crystalline cellulose in said sugar coating.

2. In a pharmaceutical tablet comprising a non-medicated, compressed core and a sugar coating, the improvement comprising incorporating a hormonal steroid and a hormonal steroid release rate controlling amount of microcrystalline cellulose in said sugar coating.

3. A pharmaceutical tablet of claim 1, in which said sugar present in said coating composition is sucrose.

4. A pharmaceutical tablet of claim 1 in which said hormonal steroid present in said sugar coating is medroxyprogesterone acetate, levonorgestrel, gestodene, medrogestone, estradiol, estriol, ethinylestradiol, mestranol,

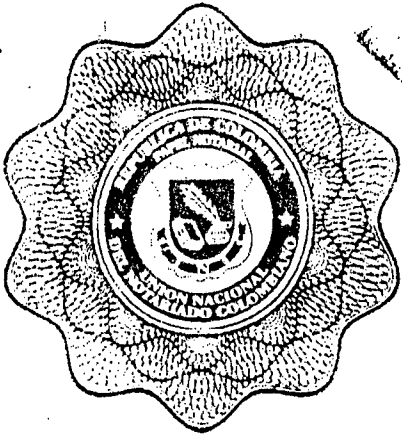
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estrone, dienestrol, hexestrol, diethylstilbestrol, progesterone, desogestrel, norgestimate, hydroxyprogesterone, norethindrone, norethindone acetate, norgestrel, megestrol acetate, methyltestosterone, ethylestrenol, methandienone, oxandrolone, trimegestone or dienogest.

5. A pharmaceutical tablet of claim 1 in which said sugar coating comprises sucrose, from about 0.1% to about 3% microcrystalline cellulose, by weight, polyvinylpyrrolidone in an amount of from 0 to about 5% by weight and a hormonal steroid in an amount of from about 0.1 to about 20% by weight.

6. A pharmaceutical tablet of claim 1 in which said sugar coat contains an estrogenic steroid and a progestogenic steroid.

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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
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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

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DELEGACIÓN DE AUTENTICACIÓN
El suscrito Notario Noveno del Circuito de Bogotá, D.C. hace constar que la copia fotostática que se adjunta es una copia exacta de la original que se encuentra en el expediente de la causa No. 1001 de 2008, de la cual se ha tomado y

31 JUL 2008

REPUBLICA DE COLOMBIA
BOGOTÁ D.C.
NOTARIO NOVENO
BOGOTÁ D.C.



16583

AA 8567152

38

promueva Lafrancol S.A., o se
promuevan contra esta y.-----
c.- Para que en todos los asuntos
arriba determinados, tanto en
los términos señalados por los
artículos 42 y complementarios
de la decisión 486 de la Comunidad Andina como del
artículo 70 del C.P.C. pueda sustituir este
mandato, transigir, conciliar, admitir los hechos del
proceso, desistir, cancelar, recibir, renunciar y
ratificar los actos de agentes oficiosos y ceder a
título gratuito y/o oneroso, licenciar, inscribir
contratos de cesión y de licencia, inscripción de
prendas, levantamiento de prendas, inscribir
derechos de retención y en general todos los asuntos
que se deban tramitar ante la Superintendencia de
Industria y Comercio.-----
Manifestamos que de la veracidad de las
declaraciones del contenido y autenticidad de los
documentos anexos en éste instrumento **NOVENO DE**
respondemos los comparecientes **BOGOTÁ, D.C. después de la** sólo
confrontación, autentico esta copia por
corresponder a la copia autentica del
documento, de la cual se ha tomado y
que se ha tenido a la vista
Bogotá, D.C.
HASTA AQUI LA MINUTA PRESENTADA **16 ABR. 2008**
REPUBLICA DE COLOMBIA
ALEXANDER PAEZ CORTE
NOTARIO NOVENO DE
BOGOTÁ, D.C.
OTORGAMIENTO Y AUTORIZACION: Leído **7** presente
instrumento Público por los comparecientes
advertidos de la formalidad de su contenido
del término legal de autenticación **REPUBLICA DE COLOMBIA**
intenciones **DILIGENCIA DE AUTENTICACION**
firmaron junto **El suscrito Notario Noveno del Circuito de**
lo autoriza. **BOGOTÁ, D.C. HACE CONSTAR que**
Se utilizaron **la copia fotostática precedida por**
las hojas de papel **la copia autenticada de que fue tomada la minuta**
AA 8567146, 8567152. **31 JUL 2008**
REPUBLICA DE COLOMBIA
NOTARIO NOVENO DE
BOGOTÁ, D.C.
REPUBLICA DE COLOMBIA
ALEXANDER PAEZ CORTE
NOTARIO NOVENO DE
BOGOTÁ, D.C.
REPUBLICA DE COLOMBIA
ALEXANDER PAEZ CORTE
NOTARIO NOVENO DE
BOGOTÁ, D.C.

DERECHOS NOTARIALES: \$ 49.600.00

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. 29.152.473

TEL: 621-2631

DIANA BEATRIZ LOPEZ

NOTARIA 33 DE BOGOTA D.C.

n.c.a.

Es segunda COPIA (FOTOCOPIA)
tomada de su original que se expide conforme al

Artículo 79 del Decreto 960 de 1970 en 06

hojas útiles con destino a Jose Luis Reyes Villamizar

Villamizar Dto. 1772/79

Santofe de Bogotá D.C. 05 JUL. 2002

Qui Almu

Como NOTARIO NOVENO DE
BOGOTÁ, D.C. Acusado de la exhibición
de una copia autenticada hecha por
el Notario de la zona, en virtud del
que se ha tomado la vista.

31 JUL 2008

DILIGENCIA DE AUTENTICACION
El suscrito Notario Noveno del Circulo de
Bogotá, D.C. HACE CONSTAR que
la copia fotostática precedente coincide
de exactamente con la fotocopia auten-
ticada de que fue tomada y que fue a
la Notaria 33 de Bogotá, D.C.
Notario Noveno - Bogotá, D.C.





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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080731

Hora Certificado 12:54:00

Operacion : 02NBM0731049

PAGINA No. 1

null

CERTIFICA:

NOMBRE: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.

DOMICILIO: CALI VALLE

DIRECCION COMERCIAL : ---K 1 46 84

DIRECCION NOTIFICACION JUDICIAL: ---K 1 46 84

CIUDAD: CALI

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

DIRECCION ELECTRONICA : esperanzacortes@lafrancol.net

AFILIADO

CERTIFICA:

NIT : 890301463-8

CERTIFICA:

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

CERTIFICA:

REFORMAS

DOCUMENTO
INS LIBRO

FECHA.DOC ORIGEN

FECHA.INS NRO.

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

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080731

Hora Certificado 12:54:00

Operacion : 02NBM0731049

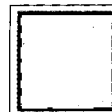
PAGINA No. 2

28406						
E.P.	101	31/01/1966	NOTARIA	CUARTA	DE	CALI 01/02/1966
31039						
E.P.	552	21/03/1968	NOTARIA	CUARTA	DE	CALI 01/04/1968
35711						
E.P.	4964	12/12/1972	NOTARIA	CUARTA	DE	CALI 16/01/1973
2975	IX					
E.P.	1956	30/05/1973	NOTARIA	CUARTA	DE	CALI 13/06/1973
4337	IX					
E.P.	4964	12/12/1972	NOTARIA	CUARTA	DE	CALI 28/11/1973
5994	IX					
E.P.	5579	12/11/1973	NOTARIA	CUARTA	DE	CALI 28/11/1973
5995	IX					
E.P.	4406	30/09/1974	NOTARIA	CUARTA	DE	CALI 28/11/1974
10887	IX					
E.P.	192	03/02/1978	NOTARIA	CUARTA	DE	CALI 14/02/1978
25355	IX					
E.P.	3479	07/09/1979	NOTARIA	CUARTA	DE	CALI 19/09/1979
34204	IX					
E.P.	4274	12/12/1984	NOTARIA	NOVENA	DE	CALI 19/12/1984
73088	IX					
E.P.	1155	21/05/1985	NOTARIA	SEPTIMA	DE	CALI 03/06/1985
76917	IX					
E.P.	1553	20/06/1986	NOTARIA	SEPTIMA	DE	CALI 08/07/1986
85997	IX					
E.P.	1458	09/06/1987	NOTARIA	SEPTIMA	DE	CALI 24/12/1987
3508	IX					
E.P.	7222	14/12/1988	NOTARIA	TERCERA	DE	CALI 19/12/1988
13847	IX					
E.P.	4530	04/09/1989	NOTARIA	TERCERA	DE	CALI 07/09/1989
21508	IX					
E.P.	3865	02/08/1990	NOTARIA	TERCERA	DE	CALI 13/08/1990
31708	IX					
E.P.	8305	13/12/1995	NOTARIA	TERCERA	DE	CALI 23/01/1996
557	IX					
E.P.	4559	16/11/1999	NOTARIA	TERCERA	DE	CALI 26/11/1999
7911	IX					
E.P.	6.004	02/12/2004	NOTARIA	TERCERA	DE	CALI 14/12/2004
13371	IX					
E.P.	6241	27/12/2006	NOTARIA	TERCERA	DE	CALI 19/01/2007
625	IX					
E.P.	389	07/02/2008	NOTARIA	TERCERA	DE	CALI 19/02/2008
1880	IX					

CERTIFICA:

VIGENCIA: 29 DE SEPTIEMBRE DEL AÑO 2057

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080731

Hora Certificado 12:54:00

Operacion : 02NBM0731049

PAGINA No. 3

CERTIFICA:

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

CERTIFICA:

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

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

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

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

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080731

Hora Certificado 12:54:00

Operacion : 02NBM0731049

PAGINA No. 4

FUNCIONES DEL GERENTE: A) ... B) 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

SEGUNDO SUPLENTE DEL GERENTE
ROBERTO M. VENTURA CRISPINO
C.C.9086003

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080731

Hora Certificado 12:54:00

Operacion : 02NBM0731049

PAGINA No. 5

PRESIDENTE

ESTHER ISABEL VENTURA DE RENDON

C.C.38979831

VICEPRESIDENTE

ROBERTO S. VENTURA PAULY

C.C.16697614

CERTIFICA:

DOCUMENTO: ACTA No. 105 DEL 09 DE NOVIEMBRE DE 2004

ORIGEN: ASAMBLEA DE ACCIONISTAS

INSCRIPCION: 17 DE FEBRERO DE 2005 No. 2032 DEL LIBRO IX

FUE(ON) 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(ON) _NOMBRADO(S)

JUNTA DIRECTIVA

PRINCIPALES

PRIMER RENGLON

ESTHER ISABEL VENTURA DE RENDON

C.C.38979831

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080731

Hora Certificado 12:54:00

Operacion : 02NBM0731049

PAGINA No. 6

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. 14675 DEL LIBRO IX

FUE(ON) NOMBRADO(S):

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

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 08 DE MAYO DE 2008
ORIGEN: ALFREDO LOPEZ & CIA LTDA
INSCRIPCION: 23 DE MAYO DE 2008 No. 5771 DEL LIBRO IX

FUE(ON) NOMBRADO(S):

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080731

Hora Certificado 12:54:00

Operacion : 02NBM0731049

PAGINA No. 7

REVISOR FISCAL PRINCIPAL

ALFREDO LOPEZ CAMPO

C.C.8241912

REVISOR FISCAL SUPLENTE

ANDERSON DAVID RODRIGUEZ REYES

C.C.16916373

CERTIFICA:

CAPITAL AUTORIZADO: \$7,500,000,000

NUMERO DE ACCIONES: 750,000,000

VALOR NOMINAL: \$10

CAPITAL SUSCRITO: \$6,000,000,000

NUMERO DE ACCIONES: 600,000,000

VALOR NOMINAL: \$10

CAPITAL PAGADO: \$6,000,000,000

NUMERO DE ACCIONES: 600,000,000

VALOR NOMINAL: \$10

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.5234- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL

UBICADO EN: ---K 1 46 84 DE CALI

RENOVO : POR EL A?O 2008

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.369809- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S A

UBICADO EN: --K 1 46A 70 DE CALI

FECHA MATRICULA : 29 DE ABRIL DE 1994

RENOVO : POR EL A?O 2008

CERTIFICA:

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080731

Hora Certificado 12:54:00

Operacion : 02NBM0731049

PAGINA No. 8

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 2008

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.734908- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL S.A
UBICADO EN: CRA. 1A NRO. 46A 28 DE CALI
FECHA MATRICULA : 28 DE MARZO DE 2008
RENOVO : POR EL A?O 2008

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.734911- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL S.A
UBICADO EN: CRA. 1B NRO. 46A 121 DE CALI
FECHA MATRICULA : 28 DE MARZO DE 2008

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.734913- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL S.A
UBICADO EN: CRA. 3 NRO. 47 25 DE CALI
FECHA MATRICULA : 28 DE MARZO DE 2008

CERTIFICA:

QUE LA SOCIEDAD EFECTUO LA RENOVACION DE SU MATRICULA MERCANTIL EL 28 DE
MARZO DE 2008 .

CERTIFICA:

QUE NO FIGURAN OTRAS INSCRIPCIONES QUE MODIFIQUEN TOTAL O PARCIALMENTE EL

*** CONTINUA ***



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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080731

Hora Certificado 12:54:00

Operacion : 02NBM0731049

PAGINA No. 9

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 31 DIAS DEL MES DE JULIO DEL A?O 2008 HORA: 12:51:48


DIEGO FERNANDO CAMPO GARCIA

