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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/565	A1	(11) International Publication Number: WO 96/19227 (43) International Publication Date: 27 June 1996 (27.06.96)
(21) International Application Number: PCT/US95/16561 (22) International Filing Date: 15 December 1995 (15.12.95) (30) Priority Data: 08/359,159 19 December 1994 (19.12.94) US (71) Applicant: ORTHO PHARMACEUTICAL CORPORATION [US/US]; Route #202, P.O. Box 300, Raritan, NJ 08869-0602 (US). (72) Inventor: GRUBB, Gary, S.; 73 Twin Oaks Road, Bridgewater, NJ 08807 (US). (74) Agents: CIAMPORCERO, Audley, A., Jr. et al.; Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933 (US).		(81) Designated States: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: CYCLOPHASIC HORMONAL REGIMEN CONTAINING ANTIPROGESTIN AND PROGESTIN		
(57) Abstract The present invention is directed to cyclophasic hormonal regimens which comprise antoprogestin and progestin for human contraception whereby progestin is administered in the alternating presence and absence of an antiprogestin in effective amounts to upregulate steroid receptor levels or is alternatively dosed with effective amounts of antiprogestin to upregulate steroid receptor levels. The present invention also provides an estrogen containing cyclophasic hormonal regimen for climacteric or menopausal hormone replacement therapy comprising the administration of an effective hormone replacement amount of estrogen in alternating doses with a combined amount of estrogen and an effective amount of antiprogestin to inhibit proliferation of endometrial tissue caused by the administration of the estrogen.		

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- 1 -

CYCLOPHASIC HORMONAL REGIMEN CONTAINING ANTIPROGESTIN AND PROGESTIN

Field of the Invention

5 The present invention is directed to cyclophasic hormonal regimens for contraception and hormone replacement therapy. More particularly, the present invention is directed to cyclophasic hormonal regimens which comprise antiprogestin and progestin for human contraception whereby progestin is continuously
10 administered in the alternating addition and absence of an antiprogestin in effective amounts to upregulate steroid receptor levels or progestin is administered in alternating doses with effective amounts of antiprogestin to upregulate steroid receptor levels. The present
15 invention also provides an estrogen containing cyclophasic hormonal regimen for climacteric or menopausal hormone replacement therapy comprising the administration of an effective hormone replacement amount of estrogen in alternating doses with a combined amount of estrogen and
20 an effective amount of antiprogestin to inhibit proliferation of endometrial tissue caused by the administration of the estrogen.

Background of the Invention

25 The concept of cyclophasic hormonal regimens comprising estrogens and progestins is disclosed by Robert Casper in U. S. Patent No. 5,108,995; 5,256,421; and 5,276,022. The disclosures of these three U. S. Patents are hereby incorporated herein by reference.

30

 The primary aim of both the oral contraception (OC) hormone replacement therapy (HRT) and cyclophasic regimens disclosed by Casper is to induce higher levels of progestin and estrogen receptors by an estrogen-induced

- 2 -

increase in receptor production. The greater concentration of steroid receptors increases the sensitivity of the target organs to progestin and estrogen and allows the use of lower doses of exogenous steroids.

5 The cyclophasic regimens of Casper upregulate the estrogen and progestin receptors in an estrogen-dominant phase of 2-4 days and then down-regulate the same receptors in a progestin-dominant phase in the next 2-4 days. In contrast to conventional oral contraception regimens which

10 are continuously progestin-dominant, the levels of the estrogen and progestin receptors are continuously down-regulated. In both phases of the cyclophasic regimen, the estrogen dose is constant while the progestin dose is varied to produce relatively progestin-dominant or

15 estrogen-dominant effects. These alternating phases continue without interruption for HRT but with OC, they are interrupted periodically for 4-7 days to allow menstrual bleeding to occur.

20 Norethindrone may be used in trials of cyclophasic phasic regimens and has a relatively short half-life. In pharmacokinetic models for contraceptive cyclophasic regimens longer half-lives for some progestin (e.g., norgestimate) given in the progestin-dominant phase is

25 observed to cause higher than intended progestin levels to extend into the estrogen-dominant phase. This effect may indicate that a sufficiently estrogen-dominant phase is not achieved and the steroid receptors are not adequately upregulated. Without adequate upregulation, the steroid

30 doses administered in a cyclophasic regimen are too low to maintain endometrial integrity and breakthrough bleeding rates higher than those resulting from administration of standard dose oral contraceptives have been observed in clinical trials.

- 3 -

An antiprogestin added to all or part of the estrogen-dominant phase of a cyclophasic regimen acts more quickly to increase the receptor levels in the estrogen-dominant phase. The mechanisms of action for this effect may be two-fold. An antiprogestin directly antagonizes the progestin receptor-binding of a progestin and prevents receptor down-regulation by the progestin. In the absence of exogenous progestin and estrogen, antiprogestins have been shown to upregulate progestin and estrogen receptors in human endometrial tissue. Following physiologic estrogen replacement in ovariectomized monkeys, antiprogestin treatment (e.g. using an antiprogestin known as RU486) induces dramatic dose-dependent rise in estradiol receptor concentrations. Despite the rise in estrogen receptor levels, an antiprogestin (RU486) inhibited endometrial proliferation and secretory activity. See Wolf et al. Fertility and Sterility, Vol 52. No. 6 December 1989 pp 1055-1060 and Neulen et al. J. Clinical Endocrinology and Metabolism, Vol. 71 No. 4, 1990 pp. 1074-1075. Low doses of an antiprogestin (10-50 mg RU486) administered in continuous or intermittent periods during the menstrual cycle inhibit ovulation. See Spitz et al. Fertility and Sterility, Vol. 59, No. 5, pp. 971-975.

It is therefore an object of the present invention to provide a cyclophasic hormonal regimen comprising the administration of antiprogestin which overcomes problems of breakthrough bleeding and/or excessive endometrial mitotic activity resulting in endometrial hyperplasia. It is an additional object of the present invention to progress beyond the prior art and provide novel cyclophasic regimens utilizing antiprogestin compounds for contraception and hormone replacement therapy. Additional objects and advantages of the invention will be set forth,

- 4 -

in part in the description which follows and in part will be obvious from the description, or may be learned by practice of the invention. The objects and advantages of the invention are realized and obtained by means of the devices, combinations, and methods particularly pointed out in the appended claims.

Summary of the Invention

To achieve the objects and purposes of the invention, as embodied and fully described herein the present invention provides a progestin and antiprogestin cyclophasic hormonal method and drug regimen for human contraception comprising the steps of: (a) administering an effective ovulation suppressing amount of a progestin in single daily doses for a period of 2-4 days; (b) administering an effective amount of an antiprogestin to upregulate steroid receptor levels in single daily doses for a period of the next 2-4 days; and (c) repeating the steps (a) and (b) for a total of 20-24 days. In preferred embodiments the method and regimen of the present invention comprises the additional steps of (d) administering no drug or a placebo for 4-8 days after the 20-24 days of drug administration; and (e) repeating steps (a-d).

25

In other embodiments of the invention a progestin, estrogen and antiprogestin cyclophasic hormonal method and drug regimen for human contraception is provided comprising the steps of: (a) administering an effective ovulation suppressing amount of a progestin and an effective breakthrough bleeding preventative amount of estrogen in a single daily dose for a period of 2-4 days; (b) administering a reduced amount of progestin and estrogen and an effective amount of an antiprogestin to

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- 5 -

upregulate steroid receptor levels in a single daily dose for a period of the next 2-4 days; and (c) repeating the steps (a) and (b) for a total of 20-24 days. In preferred embodiments the method and regimen of the invention
5 comprises the additional steps of (d) administering no drug or a placebo for 4-8 days after the 20-24 day administration of drug; and (e) repeating steps (a-d).

In other embodiments, the present invention is
10 directed to an estrogen containing cyclophasic hormonal method and regimen for climacteric or menopausal hormone replacement therapy comprising the steps of: (a) administering an effective hormone replacement amount of estrogen in single daily doses for a period of 2-4 days;
15 (b) administering the same or a reduced amount of estrogen in combination with an effective amount of antiprogesterin to inhibit proliferation of endometrial tissue caused by the administration of estrogen; and (c) repeating steps (a) and (b).

20 In further embodiments, the present invention provides a method of reducing breakthrough bleeding resulting from the administration of an effective ovulation suppressing amount of a progestin in a human
25 contraceptive regimen comprising administering the progestin for a period of 2-4 days followed by administering an effective amount of an antiprogesterin to upregulate steroid receptor levels and inhibit ovulation for a period of the next 2-4 days and repeating the above
30 cycle for a total period of 20-24 days. Preferably, no drug or placebo is administered for the next 4-8 days after the 20-24 day and the regimen is repeated.

- 6 -

Detailed Description of Preferred Embodiments of the Invention

5 Reference will now be made in detail to preferred embodiments of the invention. Examples of the preferred embodiments are illustrated in the following Examples section.

10 Particularly preferred estrogen compositions in accordance with the invention are those which comprise substantially natural human estrogens which metabolize to estradiol and estrone sulfate, particularly preferred is estropipate. Estropipate is a piperazine salt which provides a stable source of estrone sulfate.

15

The progestin compounds useful in accordance with the invention are preferably selected from the group consisting of 19-nortestosterones, particularly preferred is norethindrone. The dosing of these compositions vary with the days of administration as further described below.

20

Antiprogesterin compounds useful in accordance with the invention can be any progestin receptor antagonist or a pharmaceutically suitable agent that counteracts the normal biological activity of progestin (progesterone). A preferred antiprogesterin is a progesterone receptor antagonist, for example, mifepristone, onapristone and lilopristone are particularly suitable in the practice of this invention.

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Examples of antiprogesterins which can be employed in this invention are RU 486 ("mifepristone", Roussel Uclaf, Paris; U.S. patent 4,386,085); and "onapristone" (Schering

- 7 -

AG, Berlin; U.S. patent 4,780,461) and the steroids described in the following patents and patent applications: U.S. Patent 4,609,651, especially the compound lilopristone (11 β -(4-dimethylaminophenyl)-17 β -hydroxy-17 α -(3-hydroxy-prop-1-(Z)-enyl-4,9(10) estradien-3-one); U.S. application Serial No. 06/827,050, especially the compounds 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1-propenyl)-4,9-estradien-3-one and 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(3-hydroxy-1(2)-propenyl)-4,9-estradien-3-one; U.S. application Serial No. 07/283,632; published European patent application EP-A 04042831; and other known antiprogestins, e.g. those disclosed in U.S. Patent 4,891,368.

In preferred embodiments of the invention, the cyclophasic combination compositions are given in continuous regimens throughout the cycle and augmented by a placebo on a continuous daily basis. Such a daily continuous regimen has been found to be efficacious and is believed to aid in patient compliance whereby a patient gets into a daily routine of taking the prescribed medication without any distracting starting and stopping periods.

The purpose and desired effect of estrogen and progestin in each of contraception and HRT is well known to those skilled in the art and thus a dosage for estrogen and progestin, given the circumstance of co-administration with an antiprogestin as described herein, may be easily established by the skilled practitioner. In the case of contraception, estrogen should be administered in an effective amount to prevent breakthrough bleeding and progestin likewise should be administered in an effective amount to suppress ovulation. In the case of HRT,

- 8 -

estrogen should be administered in sufficient amounts to prevent hot flashes, reduce bone loss and reduce the risk of ischemic heart disease and progestin likewise should be administered in sufficient amounts to protect the endometrium from the stimulatory effects of estrogen. Preferred exemplative dosages in accordance with the invention include but are not limited to the following daily doses: progestin in the range of 10 to 2500 mcg, more preferably about 30 to 180 mcg for norgestimate and 350 to 1500 mcg for norethindrone; antiprogestin in the range of 1 to 100 mg; and estrogen as estradiol in the range of 0.5 to 3.0 mg for hormone replacement therapy and as ethinyl estradiol in the range of 0-50 mcg for contraceptive applications.

15

The above described dosages are generally preferred in accordance with the invention but may be varied depending upon the results of specific clinical testing, requirements of the patient, the weight and age of the patient, relative effective potency of the drug, severity of the condition being treated in light of the patients response to the drug and the particular compound or hormone combination composition being employed. The determination of optimum dosages for a particular situation is within the skill of the medical arts.

25

The estrogen, antiprogestin and progestin compositions can be administered by way of any art recognized means as practiced in the pharmaceutical arts. For example, the estrogen and progestin alone or in combination may be so formulated so that it can be administered orally, via a skin patch for transdermal absorption, by intramuscular injection, contained within an inert matrix which is implanted within the body and in

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- 9 -

a depot state, or intravaginally in a matrix that slowly releases the active compositions (such implants are taught for example in

U. S. Patent Nos. 4,957,119 and 5,088,505).

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Pharmaceutical compositions containing compounds of the invention may further comprise pharmaceutically acceptable carriers and be in either solid or liquid form. Solid form preparations include powders, tablets, dispersible granules, capsules, etc. The carrier may also be one or more substances which act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents as well as encapsulating materials. Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, peptin, dextrin, starch, methylcellulose, sodium carboxymethylcellulose, and the like. Liquid form preparations include solutions which are suitable for oral or parenteral administration, or suspensions and emulsions suitable for oral administration.

Sterile water solutions of the active component or sterile solutions of the active components in solvents comprising water, ethanol, or propylene glycol are examples of liquid preparations suitable for parenteral administration. Aqueous solutions for oral administration can be prepared by dissolving the active compound in water and adding suitable flavorants, coloring agents, stabilizers and thickening agents as required. Aqueous suspensions for oral use can be made by dispersing the active component in water together with a viscous material such as a natural or synthetic gum, methylcellulose, sodium carboxymethyl-cellulose, and other suspending agents known to the pharmaceutical formulation art. Other

- 10 -

solid dosage forms include topical dosage forms which include solutions, powders, fluid emulsions, fluid suspensions, semi-solids, ointments, pastes, creams, gels or jellies and foams; and parenteral dosage forms which
5 include solutions, suspensions, emulsions or dry powder comprising an effective amount of estrogen and progestin as taught in this invention.

Various conventional techniques for preparing
10 pharmaceutical compositions including solutions, suspensions, tablets or caplets can be employed, as would be known to those skilled in the art and as is disclosed for example by **Remington's Pharmaceutical Sciences**, Mack Publishing Co., Part 8, Chapters 76-93, *Pharmaceutical*
15 *Preparations and Their Manufacture*, pp. 1409-1677 (1985).

The pharmaceutical formulations may be provided in kit form containing preferably about 24-30, more preferably about 28 dosage form units, e.g. caplets or
20 tablets, intended for ingestion on successive days of an administration cycle. Where administration of the estrogen, progestin, and antiprogestin is intended to be periodically alternating, a plurality of caplets or tablets may be provided whereby a portion contains
25 estrogen only and the remaining tablets additionally contain progestin and antiprogestin or as is otherwise desired in accordance with the method and regimen of the invention for OC and HRT applications.

30 It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. The term "unit dosage form" as used herein refers to physically discrete units suitable as unit dosages, each

- 11 -

unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The term "doses" as used herein broadly encompasses the term unit dosage form or dosage units as well as continuous dosing of compositions by depot or other methods.

The dosages, however, may be varied depending upon the results of specific clinical testing, the requirements of the patient, the weight and age of the patient, the severity of the condition being treated, and the compound being employed. Determination of optimum dosages for a particular situation is within the skill of the art.

The invention will now be illustrated by an exemplary study involving the method of the invention. The examples are not intended to be limiting of the scope of the present invention but read in conjunction with the detailed and general description above, provide further understanding of the invention and outline a protocol for carrying out the methods of the invention for contraception in women of child bearing age or for HRT in climacteric, perimenopausal and postmenopausal women.

25

Examples

The following ingredients, procedures and medical testing are generally known and available to those skilled in the pharmaceutical and medical arts.

30

a. Study Description

The study is a randomized, controlled, double-blind, study of six contraceptive regimens and a standard oral contraceptive comparator. The

- 12 -

subjects complete a one month baseline cycle with no hormonal contraceptive to document ovulation occurred. The subjects then complete three months of the assigned oral contraceptive regimen during which indicators of ovulation, laboratory measures and menstrual bleeding patterns are assessed.

b. Materials and Supplies

Test medication are supplied as follows for the progestin, i.e. norgestimate (NGM), the estrogen, i.e. ethinyl estradiol (EE) and the antiprogesterin, i.e. mifepristone or RU486 (RU):

Table 1. Experimental CYCLOPHASIC Regimens in Protocol for Contraception

		<u>Example 1</u>			<u>Example 2</u>			<u>Example 3</u>		
		NGM	EE	RU	NGM	EE	RU	NGM	EE	RU
		mcg	mcg	mg	mcg	mcg	mg	mcg	mcg	mg
20	Progestin phase ¹	180	20	0	180	20	0	180	20	0
25	Estrogen phase ²	30	10	10	30	0	25	0	0	25
		<u>Example 4</u>			<u>Example 5</u>					
		NGM	EE	RU	NGM	EE	RU			
		mcg	mcg	mg	mcg	mcg	mg			
30	Progestin phase ¹	180	0	0	180	0	0			
35	Estrogen phase ²	30	0	25	0	0	25			

¹Cycle days 1-2, 5-6, 9-10, 13-14, 17-18, 21-22

²Cycle days 3-4, 7-8, 11-12, 15-16, 19-20

- 13 -

A comparator regimen of 20 mcg EE + 180 mcg NGM alternating every 2-4 days with 20 mcg EE + 30 mcg NGM is included.

5 c. Study Population

10 The study population for regimens 1-5 and comparator regimen are healthy premenopausal women of childbearing age protected from pregnancy by use of barrier contraception, sterilization or abstinence.

 d. Methods - Ovulation and Lipid Measurement

15 All clinical laboratory evaluations are standard industry tests which may be performed by a central laboratory.

 e. Results

20 With a lower dose of EE compared to the standard cyclophasic contraceptive regimen, a lowering of estrogen-related side effects (e.g., nausea, weight gain, bloating, headaches) would result. The lower EE dose would also have changes in several laboratory measures indicating lower blood coagulability and hepatic enzyme elevation.

25

 f. Discussion

30 An antiprogestin can complement (example 1) or substitute for (example 2) an estrogen during the estrogen dominant phase in a cyclophasic regimen by inducing an increase in steroid receptor concentrations as an estrogen dose. An antiprogestin may also stabilize the

- 14 -

proliferative endometrium allowing the elimination of estrogen during the progestin-dominant phase (examples 4 and 5). An antiprogestin can also function similarly to a progestin by inhibiting ovulation and stabilizing proliferative endometrium to reduce breakthrough bleeding. Therefore, an antiprogestin can substitute for a progestin in the estrogen-dominant phase (examples 3 and 5).

10

Examples 6-8a. Study Description

The study is a randomized, controlled, double-blind, study of three hormone replacement therapy (HRT) regimens and a standard cyclophasic HRT comparator. The subjects will complete six months of the assigned HRT regimen during which symptom frequency, bleeding patterns and laboratory measures will be assessed.

20

b. Materials and Supplies

Table 2. Experimental CYCLOPHASIC Regimens in Protocol for Hormone Replacement Therapy

25

	<u>Example 6</u>			<u>Example 7</u>			<u>Example 8</u>		
	NGM	EP	RU	NGM	EP	RU	NGM	EP	RU
	mcg	mg	mg	mcg	mg	mg	mcg	mg	mg
30 Progestin phase ¹	90	2	0	90	2	0	0	2	0
Estrogen phase ²	0	2	10	0	1	25	0	2	10

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¹Alternating two day intervals (i.e. days 1-2, 5-6, 9-10, 13-14, 17-18, 21-22, etc.)

²Alternating two day intervals (i.e. days 3-4, 7-8, 11-12, 15-16, 19-20, etc.)

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- 15 -

A comparator regimen of 2 mg EP alternating every two days with 2 mg EP + 90 mcg NGM would be included.

5 c. Study Population

The study population for regimens 6-8 and comparator regimen are healthy perimenopausal and postmenopausal women 40 years or older.

10 d. Methods - Lipid Measurement

All clinical laboratory evaluations are standard industry tests which may be performed by a central laboratory.

15 e. Results

Menopausal symptoms, irregular bleeding and lipid changes will be improved by the addition of an antiprogestin to a standard cyclophasic HRT regimen. The standard cyclophasic regimen doses of estrogen and progestin can be reduced and clinical benefits maintained with the addition of an antiprogestin.

20 f. Discussion

25 The addition of an antiprogestin to the cyclophasic regimen potentiates the action of the estrogen and progestin by augmenting the steroid receptor increase induced by the standard cyclophasic estrogen dose (example 6). The antiprogestin allows a reduction in
30 the estrogen dose (example 7) without a decrease in the beneficial clinical effects. The ability of the antiprogestin to reduce endometrial mitotic activity allows the antiprogestin to substitute for the progestin in preventing endometrial hyperplasia

- 16 -

(example 8), without having the adverse lipid effects of the progestin.

5 The scope of the present invention is not limited by the description, examples and suggested methods described herein and modifications can be made without departing from the spirit of the invention. For example, other estrogens and progestins may be substituted for those provided in the examples herein to achieve similar
10 advantageous results.

15 Applications of the compositions, protocols and methods of the present invention can be accomplished by any pharmaceutical and/or medical methods and techniques as are presently or prospectively known to those skilled in the art. It is intended that the invention cover any modifications and variations of this invention provided that they come within the scope of the appended claims and their equivalents.

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- 17 -

What is claimed is:

1. A progestin and antiprogestin cyclophasic hormonal
5 method and regimen for human contraception comprising
the steps of:
 - a) administering an effective ovulation suppressing
amount of a progestin in single daily doses for
a period of 2-4 days;
 - 10 b) administering an effective amount of an
antiprogestin to upregulate steroid receptor
levels in single daily doses for a period of the
next 2-4 days; and
 - c) repeating steps a and b for a total of 20-24
15 days.
2. The regimen of claim 1 comprising the additional
steps of
 - d) administering no drug or a placebo for 4-8 days;
 - 20 and
 - e) repeating steps a-d.
3. The method of claim 1 wherein the progestin is a 19-
nortestosterone and the antiprogestin is selected
25 from the group consisting of mifepristone,
onapristone and lilopristone.
4. The method of claim 1 wherein the progestin
administered is norgestimate in a dosage range of
30 about 10-250 mcg per day or norethindrone in a dosage
range of about 350-2500 mcg per day and the dosage of
antiprogestin provided is from about 1 to 100 mg per
day.

- 18 -

5. The method of claim 1 wherein the regimen comprises
- a) administering an effective ovulation suppressing amount of a progestin in single daily doses for 2 days;
 - 5 b) administering an effective amount of an antiprogestin to upregulate steroid receptor levels in single daily doses for a period of the next 2 days; and
 - c) repeating steps a and b for a total of 22 days.
- 10
6. The method of claim 5 wherein the progestin administered is norgestimate in a dosage range of about 10-250 mcg per day or norethindrone in a dosage range of about 350-2500 mcg per day and the dosage of
- 15 antiprogestin provided is from about 1 to 100 mg per day.
7. A progestin, estrogen and antiprogestin cyclophasic hormonal method and regimen for human contraception comprising the steps of:
- 20
- a) administering an effective ovulation suppressing amount of a progestin and an effective breakthrough bleeding preventative amount of estrogen in a single daily dose for a period of
 - 25 2-4 days;
 - b) administering a reduced amount of progestin and estrogen and an effective amount of an antiprogestin to upregulate steroid receptor levels in a single daily dose for a period of
 - 30 the next 2-4 days; and
 - c) repeating the steps a and b for a total of 20-24 days.
8. The regimen of claim 7 comprising the additional

- 19 -

steps of

- d) administering no drug or a placebo for 4-8 days;
and
- e) repeating steps a-d.

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9. The method of claim 7 wherein the estrogen is ethinyl estradiol, the progestin is a 19-nortestosterone, and the antiprogestin is selected from the group consisting of mifepristone, onapristone and lilopristone.

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10. The method of claim 7 wherein the estrogen is ethinyl estradiol administered in a dosage range of about 2 - 30 mcg per day, the progestin administered is norgestimate in a dosage range of about 10-250 mcg per day or norethindrone in a dosage range of about 350-2500 mcg per day and the dosage of antiprogestin provided is from about 1 to 100 mg per day.

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- 20 11. An estrogen, progestin and antiprogestin cyclophasic hormonal regimen for climacteric or menopausal hormone replacement therapy comprising the steps of:
- a) administering an effective hormone replacement amount of estrogen in single daily doses for a period of 2-4 days;
 - 25 b) administering a reduced amount of estrogen in combination with an effective amount of antiprogestin or combination of progestin and antiprogestin to inhibit proliferation of endometrial tissue caused by the administration of estrogen for a period of 2-4 days; and
 - 30 c) repeating steps a and b.

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12. The method of claim 11 wherein the estrogen

- 20 -

composition comprises substantially natural human estrogens which metabolize to estradiol and estrone sulfate.

- 5 13. The method of claim 11 wherein the estrogen is estropipate and the progestin is norethindrone, the anti-progestin is selected from the group consisting of mifepristone, onapristone and lilopristone.
- 10 14. The method of claim 11 wherein the estrogen administered is estropipate in a dosage range of about 0.5 - 3.0 mg per day, the progestin administered is norethindrone in a dosage range of about 100 - 1500 mcg per day and the antiprogestin is provided in a dosage range from about 1 - 100 mg per day.
- 15
15. The method of claim 11 wherein the regimen comprises:
- 20 a) administering an effective hormone replacement amount of estrogen in single daily doses for a period of 4 days;
- 25 b) administering a reduced amount of estrogen in combination with an effective amount of antiprogestin or combination of progestin and antiprogestin to inhibit proliferation of endometrial tissue caused by the administration of estrogen for a period of 3 days; and
- 30 c) repeating steps a and b.
16. The method of claim 15 wherein the estrogen administered is estropipate in a dosage range of about 0.5 - 3.0 mg per day, the progestin administered is norethindrone in a dosage range of about 100 - 1500 mcg per day and the antiprogestin is

- 21 -

provided in a dosage range from about 1 - 100 mg per day.

- 5 17. A method of reducing breakthrough bleeding in a human contraceptive regime comprising the steps of:
- a) the administration of an effective ovulation suppressing amount of a progestin for a period of 2-4 days;
 - 10 b) administering an effective amount of an antiprogestin to upregulate steroid receptor levels and inhibit ovulation levels for a period of the next 2-4 days; and
 - c) repeating the above cycle for a total period of 20-24 days.
- 15 18. The regime of claim 17 comprising the additional steps of:
- d) administering no drug or placebo of 4 - 8 days; and
 - 20 e) repeating steps a) - d).
- 25 19. The method of claim 17 wherein the estrogen is ethinyl estradiol, the progestin is a 19-nortestosterone and the antiprogestin is selected from the group consisting of mifepristone, onapristone and lilopristone.
- 30 20. The method of claim 17 wherein the estrogen is ethinyl estradiol administered in a dosage range of about 2 - 30 mcg per day, the progestin administered is norgestimate in a dosage range of about 10-250 mcg per day or norethindrone in a dosage range of about 350-2500 mcg per day and the dosage of antiprogestin provided is from about 1 to 100 mg per day.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/16561

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/565

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FERTIL STERIL, OCT 1993, 60 (4) P610-5, UNITED STATES, XP000569447 KEKKONEN R ET AL: "Sequential regimen of the antiprogesterone RU486 and synthetic progestin for contraception." see abstract	1-20
A	--- FERTIL STERIL, APR 1990, 53 (4) P747-50, UNITED STATES, XP000569448 KEKKONEN R ET AL: "Interference with ovulation by sequential treatment with the antiprogesterone RU486 and synthetic progestin." see page 749, line 2, paragraph 7 - page 750, line 1, paragraph 1 --- -/--	1-20

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

☒ Patent family members are listed in annex.

* Special categories of cited documents:

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

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

Date of the actual completion of the international search

10 May 1996

Date of mailing of the international search report

24.05.96

Name and mailing address of the ISA

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Authorized officer

Leherte, C

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/US 95/16561

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,93 17686 (SCHERING AG) 16 September 1993 see claims ---	1-20
A	WO,A,93 21927 (MEDICAL COLLEGE OF HAMPTON ROA ;HODGEN GARY D (US)) 11 November 1993 see claims ---	1-20
A	WO,A,94 04156 (AKZO NV ;BERGINK ENGELBERT WILLEM (NL)) 3 March 1994 see abstract -----	1-20

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US95/16561

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims searched incompletely: 1-2, 4-8, 11-12, 15-18, 20
In view of the large number of compounds which are defined by the wording of the claims, the search has been performed on the general idea and compounds mentioned in the examples of the description.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/US 95/16561

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9317686	16-09-93	CA-A-	2134961	03-09-93
		CZ-A-	9402111	13-12-95
		EP-A-	0630246	28-12-94
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		JP-T-	7509218	12-10-95
		NO-A-	943234	01-11-94
		ZA-A-	9301492	23-12-93

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		CN-A-	1079651	22-12-93
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		FI-A-	945207	04-11-94
		NO-A-	944210	04-11-94
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WO-A-9404156	03-03-94	AU-B-	4708993	15-03-94
		ZA-A-	9305617	07-03-94
