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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

ORTHO-McNEIL PHARMACEUTICAL, INC.,
Route 202
Raritan, NJ 08869

Plaintiff,

vs.

BARR LABORATORIES, INC.
2 Quaker Road
Pomona, NY 10970

Defendant.

Civil Action No. 00-2805 (GEB)

COMPLAINT

Plaintiff Ortho-McNeil Pharmaceutical, Inc. (previously known as Ortho Pharmaceutical Corporation) (hereinafter "Ortho") for its Complaint against defendant Barr Laboratories, Inc. ("Barr") alleges as follows:

JURISDICTION AND PARTIES

1. This is a civil action for patent infringement arising under the patent laws of the United States, 35 U.S.C. §§ 271(c)(2) and 21 U.S.C. § 355.

2. Jurisdiction and venue are proper in this judicial district pursuant to Title 35 U.S.C., 28 U.S.C. §§ 1331, 1338(a) and 1400(b).

3. Plaintiff Ortho is a corporation organized and existing under the laws of the State of Delaware having its principal place of business at U.S. Route 202, Raritan, New Jersey.

4. Defendant Barr is a corporation organized and existing under the laws of the State of New York, and having its principal offices at 2 Quaker Road, Pomona, NY.

COUNT I
(Patent Infringement)

5. On July 23, 1985, United States Patent No. 4,530,839 entitled "TRIPHASIC ORAL CONTRACEPTIVE" was duly and legally issued (the "'839 patent"). Since that date, Ortho has been and still is the owner of this Patent. (A copy of the '839 patent is attached hereto as Exhibit A).

6. On October 1, 1985, United States Patent No. 4,544,554 entitled "TRIPHASIC ORAL CONTRACEPTIVE" was duly and legally issued (the " '554 patent"). Since that date, Ortho has been and still is the owner of this Patent. (A copy of the '554 patent is attached hereto as Exhibit B).

7. On October 7, 1987, United States Patent No. 4,616,006 entitled "TRIPHASIC ORAL CONTRACEPTIVE" was duly and legally issued (the " '006 patent"). Since that date, Ortho has been and still is the owner of this Patent. (A copy of the '006 patent is attached hereto as Exhibit C).

8. R.W. Johnson Pharmaceutical Research Institute ("PRI"), an unincorporated division of Ortho, is the holder of an approved New Drug Application ("NDA") under Section 505(a) of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(a), for a combination of norgestimate and ethinyl estradiol (ORTHO TRI-CYCLEN® -21 and -28), and their use covered by the '839, '554 and '006 patents.

9. Barr has filed an Abbreviated New Drug Application ("ANDA") No. 75-808 for norgestimate and ethinyl estradiol pursuant to 21 Section 505(j) of the FFDCA, seeking approval to engage in the commercial manufacture, use and sale of norgestimate and ethinyl estradiol before the expiration of the '839, '554 and '006 patents. Barr's request for approval under the ANDA comprises practices within the claims of the aforesaid '839, '554 and '006 patents.

10. As part of its ANDA filing, Barr has provided written certification to the Food and Drug Administration that the claims of the '839, '554 and '006 patents are invalid, as called for by Section 505(j)(2)(A)(vii)(IV) of the FFDCA.

11. By letter to Johnson & Johnson, Ortho's parent, dated April 26, 2000, Barr gave written notice of its certification of invalidity of the '839, '554 and '006 patents, alleging that the '839, '554 and '006 patents are invalid and informing Ortho that Barr seeks approval to market norgestimate and ethinyl estradiol prior to the expiration of the aforesaid patents.

12. Under Title 35 U.S.C. § 271(e)(2), Barr's actions described in Paragraphs 9-11 above constitute infringement of claims 2, 3 and 7 of the '839 patent, claim 10 of the '554 patent, and claims 7 and 9 of the '006 patent.

WHEREFORE, plaintiff Ortho prays for judgment:

1. Awarding Ortho a final injunction enjoining Barr and its officers, agents, servants, and employees from any commercial manufacture, use or sale of an approved drug which infringes claims 2, 3 and 7 of U.S. Patent No. 4,530,839, claim 10 of United States Patent No. 4,544,554, and/or claims 7 and 9 of United States Patent No. 4,616,006;

2. Ordering that the effective date of any approval or use of Barr's application under Section 505(j) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j) for a combination of norgestimate and ethinyl estradiol or their equivalents be not earlier than the expiration date of United States Patent No. 4,530,839, United States Patent No. 4,544,554 and United States Patent No. 4,616,006;

3. Awarding Ortho its damages; and

4. Awarding Ortho its reasonable attorneys' fees, costs of this action, and such other and further relief as this Court may deem just and proper.

Respectfully submitted,

Dated: June 9, 2000

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CERTIFICATION PURSUANT TO L.CIV.R. 11.2

I hereby certify that to my knowledge the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding, except that a patent infringement action involving the patents that are at issue in this action, *Ortho-McNeil Pharamceutical, Inc. v. Barr Laboratories, Inc.*, Civil Action No. 99-CV-235 (GEB), is pending before the Hon. Garrett E. Brown, Jr.

William J. Brennan, III

Exhibit A

United States Patent [19]

Pasquale

[11] **Patent Number: 4,530,839**

[45] **Date of Patent: Jul. 23, 1985**

[54] **TRIPHASIC ORAL CONTRACEPTIVE**

[75] Inventor: Samuel A. Pasquale, Basking Ridge, N.J.

[73] Assignee: Ortho Pharmaceutical Corporation, Raritan, N.J.

[21] Appl. No.: 536,135

[22] Filed: Sep. 26, 1983

[51] Int. Cl.³ A01N 45/00

[52] U.S. Cl. 514/171; 514/843

[58] Field of Search 424/238, 241, 239

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,291,028 9/1981 Vorys 424/238

4,378,356 3/1983 De Jager 424/238

Primary Examiner—Elbert L. Roberts

Attorney, Agent, or Firm—Benjamin F. Lambert

[57] **ABSTRACT**

A method of contraception in which an estrogen and a progestogen are administered daily for 21 days, the first seven days at a low contraceptively effective daily dose, the next 7 days at a daily progestogen dose about 1.5–2 times that of the first 7 days, and the next 7 days at a daily progestogen dose of 2–2.5 times that of the first 7 days, provided that the dosage of the estrogen is maintained at a constant level for the entire 21 days.

9 Claims, No Drawings

United States Patent [19]

Pasquale

[11] **Patent Number: 4,530,839**

[45] **Date of Patent: Jul. 23, 1985**

[54] **TRIPHASIC ORAL CONTRACEPTIVE**

[75] Inventor: **Samuel A. Pasquale, Basking Ridge, N.J.**

[73] Assignee: **Ortho Pharmaceutical Corporation, Raritan, N.J.**

[21] Appl. No.: **536,135**

[22] Filed: **Sep. 26, 1983**

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[58] Field of Search 424/238, 241, 239

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[57] **ABSTRACT**

A method of contraception in which an estrogen and a progestogen are administered daily for 21 days, the first seven days at a low contraceptively effective daily dose, the next 7 days at a daily progestogen dose about 1.5–2 times that of the first 7 days, and the next 7 days at a daily progestogen dose of 2–2.5 times that of the first 7 days, provided that the dosage of the estrogen is maintained at a constant level for the entire 21 days.

9 Claims, No Drawings

ORTHO EX 9

TRIPHASIC ORAL CONTRACEPTIVE

This invention relates to a method of contraception comprising the oral administration of a low but contraceptively effective daily dosage of an estrogen and a progestogen for 21 successive days.

Oral contraceptives first became available in the early 1960's. Through continued research, new lower-dose estrogen products of high effectiveness have been developed. The oral administration of combination type preparations containing estrogens and progestogens has been known for some time. The administration of purely sequential preparations wherein an estrogen is administered at a high dosage in the absence of a gestagen, over a period of 7 days, and thereafter the estrogen is administered at the same high dosage in combination with a relatively high amount of a progestogen over a period of 15 days, with the next 6 days being a blank period without administration of estrogen or progestogen in order to mimic the normal 28-day menstrual cycle of the woman, is also known.

Two stage or bi-phasic combination type oral contraceptives, wherein a combination of an estrogen at a low dosage and a progestogen at a low dosage first being administered for 10–12 days and subsequently a combination of the same dosage of estrogen and a dosage of progestogen increased to 2–3 times as much is administered for 11–9 days, were developed in an effort to reduce dosage and keep bleeding patterns at an acceptable level. This sequence is generally followed by a 5–7 day hormone-free period during which no estrogen or progestogen is ingested in an effort to adapt to the normal 28-day female cycle.

One disadvantage inherent in the administration of the aforementioned pure and modified sequential products involving the administration of relatively high doses of estrogen, in addition to the usual symptoms due to excessive estrogen, i.e., gastrointestinal disturbances, nausea, weight gain with formation of edema, etc., is an increase in the risk of thromboembolic disease. Many of these disadvantages can be avoided by the administration of the above-described two-stage combination contraceptives, but even in the two-stage products it would be desirable if the compatibility and/or the control of the cycle could be improved.

It is also known to administer three-stage combination type oral contraceptives wherein a low contraceptively effective daily dose of an estrogen and a progestogen are administered for the first 4–6 days, and for the next 4–6 days a daily estrogen dose 1–2 times and a daily progestogen dose 1–1.5 times that of the first 4–6 days and for the next 9–11 days at a daily estrogen dose from that of the first 4–6 days to that of the next 4–6 days and a daily progestogen dose higher than either prior daily dose, up to 3 times that of the initial dose. (See U.S. Pat. No. 3,957,982). In this regimen, however, the dosage of both the estrogen and the progestogen is varied during the 21-day cycle.

In recent years data collected on the use of various oral contraceptive regimens have indicated that increased blood pressure and decreased glucose tolerance are associated with the progestogen content or progestational activity of oral contraceptives. In addition, the progestogen activity is associated with a decrease in serum high density lipoprotein values. These findings have prompted a greater emphasis on a reduction of the progestogen dosage in oral contraceptives.

There is a need, therefore, for a combination type contraceptive which contains low concentrations of estrogen and progestogen but is still effective for the prevention of pregnancy.

By the present invention a triphasic oral contraceptive regimen is provided wherein the estrogen dosage is kept constant throughout the 21-day cycle while the progestogen dosage is gradually increased in successive doses. The purpose of the invention is to lower total monthly steroid dose in the oral contraceptive while still obtaining equivalent bleeding patterns and protection against pregnancy as found with conventional oral contraceptives.

According to the present invention, reliable contraception is achieved by administering for 21 successive days to a female a combination of an estrogen and a progestogen, for the first 7 days in a contraceptively effective daily dosage of about 0.125–0.75 mg of a progestogen in combination with about 0.02–0.05 mg of an estrogen; for the next 7 days, in a daily dosage of about 0.50–1.0 mg of a progestogen together with about 0.02–0.50 mg of an estrogen; and for the last 7 days a daily dosage of about 0.75–2.0 mg of a progestogen in combination with about 0.02–0.05 mg of an estrogen, provided that the dosage of estrogen is kept constant in each phase during the 21-day cycle. The actual weight amount of the dosage at each dosage level will depend upon the estrogenic and progestogenic activity, respectively, of the components selected for the dosage units.

The total number of days during which the progestogen and estrogen combinations are administered daily is 21. These are followed by 7 days which are free of hormone administration to approximate the natural 28-day menstrual cycle of the female. In actual practice a placebo or any other hormone-free agent such as, for example, iron supplements, may be administered during this period.

The contraceptive composition employed in the present invention comprises 21 separate daily dosage units which are adapted for successive daily oral ingestion. In a preferred embodiment, the composition consists essentially of, as the first phase, 7 dosage units containing, in admixture with a pharmaceutically acceptable carrier, a combination of about 0.035 mg of an estrogen in combination with 0.5 mg of progestogen, followed by, as the second phase, 7 dosage units containing, in admixture with a pharmaceutically acceptable carrier, a combination of 0.035 mg of an estrogen and 0.75 mg of a progestogen, followed by, as the third phase, 7 dosage units containing in admixture with a pharmaceutically acceptable carrier a combination of 0.035 mg of an estrogen and 1.0 mg of a progestogen.

Any conventional estrogen may be employed as a suitable component in the contraceptive regimen of this invention. The particular regimen employed in a daily dosage should be equal in contraceptive activity in each phase to a daily dosage of about 0.020–0.050 mg of 17α-ethinylestradiol. The preferred dosage is one equal to a daily dosage of about 0.035 mg of 17α-ethinylestradiol.

In addition to 17α-ethinylestradiol, esters and ethers of 17α-ethinylestradiol may also be employed as the estrogen component. Natural estrogens such as estrone, estradiol and estriol, and their esters, as well as the synthetic estrogens, may also be employed. The preferred estrogen is 17α-ethinylestradiol.

As the progestogen component, any progestationally active compound may be employed. The progestogen is

preferably administered in a daily dosage in the first 7 days corresponding in progestogenic activity to 0.125–0.75 mg of norethindrone per day, during the next 7 days a daily dosage corresponding in progestogenic activity to 0.50–1.0 mg of norethindrone per day and during the last 7 days a daily dosage corresponding in progestogenic activity to 0.75–2.0 mg of norethindrone per day.

Progestogens which may be employed as a component in the present invention include progesterone and its derivatives such as, for example, 17-hydroxyprogesterone esters and 19-nor-17-hydroxyprogesterone esters, 17α-ethinyltestosterone, 17α-ethinyl-19-nortestosterone and derivatives thereof, norethindrone, and D-17β-acetoxy-13β-ethyl-17α-ethinyl-gon-4-en-3-one oxime. The preferred progestogens are norethindrone, d-norgestrel and D-17β-acetoxy-13β-ethyl-17α-ethinyl-gon-4-en-3-one oxime.

The estrogen and progestogen components are preferably administered together orally, but they can also be administered separately or parenterally. In general, the effective agents are processed, together with the usual additives, vehicles and/or flavor-ameliorating agents normally employed in Galenic pharmacy, in accordance with generally accepted pharmaceutical practices. For the preferred oral administration, tablets, dragees, capsules, pills, suspensions or solutions are particularly suitable; for parenteral application, oily solutions such as, for example, sesame oil or castor oil solutions which can optionally additionally contain a diluent such as, for example, benzyl benzoate or benzyl alcohol.

In the case of the preferred oral application, the three-phase combination-type contraceptives are preferably packaged in the form of a pharmaceutical kit or package in which the daily dosages are arranged for proper sequential administration. This invention also relates, therefore, to pharmaceutical packages which contain combination-type contraceptives in 28 dosage units in a synchronized, fixed sequence, wherein the sequence or arrangement of the dosage units corresponds to the stages of daily administration.

The pharmaceutical package can be, e.g., in the form of a transparent package having 28 dosage units arranged sequentially and consisting of 7 tablets for the first phase, followed by 7 tablets for the second phase, followed by 7 tablets for the third phase, and finally followed by 7 placebos. A single tablet is to be taken each day over a period of 28 days.

Without further elaboration it is believed that one skilled in the art, using the preceding description, can fully utilize the present invention. The following preferred specific embodiments are to be construed as merely illustrative of the invention and are not meant to limit the invention in any way.

EXAMPLE 1

Composition of a tablet for each stage:

1st Stage 7 Tablets

0.036	mg.	17α-ethinylestradiol
0.50	mg.	norethindrone
88.9	mg.	lactose anhydrous DT
10.0	mg.	pregelatanized starch N.F.
0.5	mg.	magnesium stearate N.T.
99.936	mg.	total weight

2nd Stage 7 Tablets

0.036	mg.	17α-ethinylestradiol
0.75	mg.	norethindrone
88.70	mg.	lactose anhydrous DT
10.02	mg.	pregelatanized starch N.F.
0.5	mg.	magnesium stearate N.T.
100.06	mg.	total weight

3rd Stage 7 Tablets

0.036	mg.	17α-ethinylestradiol
1.0	mg.	norethindrone
88.5	mg.	lactose anhydrous DT
10.0	mg.	pregelatanized starch N.F.
0.5	mg.	magnesium stearate N.T.
100.036	mg.	total weight

EXAMPLE 2

Composition of a tablet for each stage:

1st Stage 7 Tablets

0.036	mg.	17α-ethinylestradiol
0.50	mg.	D-17β-acetoxy-13β-ethyl-17α-ethinyl-gon-4-en-3-one oxime
87.9	mg.	lactose anhydrous DT
11.1	mg.	pregelatanized starch N.F.
0.5	mg.	magnesium stearate N.T.
100.036	mg.	total weight

2nd Stage 7 Tablets

0.036	mg.	17α-ethinylestradiol
0.75	mg.	D-17β-acetoxy-13β-ethyl-17α-ethinyl-gon-4-en-3-one oxime
89.70	mg.	lactose anhydrous DT
9.02	mg.	pregelatanized starch N.F.
0.5	mg.	magnesium stearate N.T.
100.006	mg.	total weight

3rd Stage 7 Tablets

0.036	mg.	17α-ethinylestradiol
1.0	mg.	D-17β-acetoxy-13β-ethyl-17α-ethinyl-gon-4-en-3-one oxime
87.5	mg.	lactose anhydrous DT
11.0	mg.	pregelatanized starch N.F.
0.5	mg.	magnesium stearate N.T.
100.036	mg.	total weight

EXAMPLE 3

Composition of a tablet for each stage:

1st Stage 7 Tablets

0.035	mg.	17α-ethinylestradiol
0.50	mg.	d-norgestrel
90.0	mg.	lactose anhydrous DT
9.0	mg.	pregelatanized starch N.F.
0.5	mg.	magnesium stearate N.T.
100.035	mg.	total weight

2nd Stage 7 Tablets

0.035	mg.	17α-ethinylestradiol
0.75	mg.	d-norgestrel
87.70	mg.	lactose anhydrous DT
11.02	mg.	pregelatanized starch N.F.
0.5	mg.	magnesium stearate N.T.
100.005	mg.	total weight

3rd Stage 7 Tablets

0.035	mg.	17α-ethinylestradiol
1.0	mg.	d-norgestrel
89.5	mg.	lactose anhydrous DT
9.0	mg.	pregelatanized starch N.F.
0.5	mg.	magnesium stearate N.T.
100.035	mg.	total weight

Clinical Tests

EXAMPLE 4

A preparation according to Example 1 was administered in three separate studies to a total of 656 women of child-bearing age. Subjects meeting the selection criteria were administered the contraceptive formulation on a regimen of 21 days on medication and 7 days off for up to 12 cycles.

The preparation was shown to be highly efficacious in preventing pregnancy. In each study the bleeding pattern consistently showed a decrease in the incidence of midcycle breakthrough bleeding and/or spotting.

Having described the invention in specific detail and exemplified the manner in which it may be carried into practice, it will be apparent to those skilled in the art that innumerable variations, applications, modifications, and extensions of the basic principles involved may be made without departing from its spirit or scope. It is to be understood that the foregoing is merely exemplary and the present invention is not to be limited to the specific form or arrangements of parts herein described and shown.

I claim:

1. A method of contraception which comprises administering for 21 successive days to a female of childbearing age a combination of an estrogen and a progestogen in a low but contraceptively effective daily dosage corresponding in estrogenic activity to 0.02–0.05 mg of 17α-ethinylestradiol and in progestogenic activity to 0.125–0.75 mg of norethindrone for 7 days; for the next 7 days an estrogen daily dosage equal to 0.02–0.05 mg of 17α-ethinylestradiol and in progestogenic activity to 0.50–1.0 mg of norethindrone; and for the next 7 days an estrogen daily dosage equal to 0.02–0.05 mg of 17α-ethinylestradiol and in progestogenic activity of 0.75–2.0 mg of norethindrone; followed by 7 days without estrogen and progestrogen administration, provided that the estrogen daiy dosage is the same for each 7 day period.

2. The method of claim 1 wherein the estrogen and progestogen are administered orally.

3. The method of claim 1 wherein the estrogen and progestogen are administered in admixture.

4. The method of claim 1 wherein the progestogen is selected from d-norgestrel, norethindrone, progesterone and D-17β-acetoxy-13β-ethyl-17α-ethinyl-gon-4-en-3-one oxime.

5. The method of claim 1 wherein the estrogen is selected from 17α-ethinylestradiol, estrone, estradiol and estriol.

6. The method of claim 1 wherein the estrogen is 17α-ethinylestradiol and the progestogen is norethindrone.

7. The method of claim 1 wherein the estrogen is 17α-ethinylestradiol and the progestogen is D-17β-acetoxy-13β-ethyl-17α-ethinyl-gon-4-en-3-one oxime.

8. The method of claim 1 wherein the estrogen daily dosage is 0.035 mg for each 7 day period and the progestogen daily dosage is 0.5 mg for the first 7 days, 0.75 mg for the second 7 days and 1.0 mg for the third 7 days.

9. The contraception method of claim 1 which comprises administering for 21 successive days to a female of childbearing age a combination of 17α-ethinylestradiol and norethindrone in a contraceptively effective daily dosage corresponding to 0.035 mg of 17α-ethinylestradiol and 0.50 mg of norethindrone for 7 days; for the next 7 days a daily dosage equal to 0.035 mg of 17α-ethinylestradiol and 0.75 mg of norethindrone; and for the next 7 days a daily dosge equal to 0.035 mg of 17α-ethinylestradiol and 1.0 mg of norethindrone; followed by 7 days without estrogen and progestogen administration.

* * * * *

Exhibit B

United States Patent [19]

Pasquale

[11] **Patent Number: 4,544,554**

[45] **Date of Patent: * Oct. 1, 1985**

[54] TRIPHASIC ORAL CONTRACEPTIVE

[75] Inventor: Samuel A. Pasquale, Basking Ridge, N.J.

[73] Assignee: Ortho Pharmaceutical Corporation, Raritan, N.J.

[*] Notice: The portion of the term of this patent subsequent to Jul. 23, 2002 has been disclaimed.

[21] Appl. No.: 607,038

[22] Filed: May 4, 1984

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 536,135, Sep. 26, 1983.

[51] Int. Cl.[4] A61K 31/56

[52] U.S. Cl. 514/170; 514/182; 514/177

[58] Field of Search 424/238, 241, 243

[56] References Cited

U.S. PATENT DOCUMENTS

4,291,028 9/1981 Vorys 424/238

4,378,356 3/1983 De Jager 424/238

Primary Examiner—Elbert L. Roberts

Attorney, Agent, or Firm—Benjamin F. Lambert

[57] ABSTRACT

A method of contraception in which an estrogen and a progestogen are administered daily in a three phase sequence for 21 days is disclosed. In the first phase a combination of an estrogen and a progestogen in a low but contraceptively effective daily dosage corresponding in estrogenic activity to 0.02–0.05 mg of 17α-ethinylestradiol and in progestogenic activity to 0.065–0.75 mg of norethindrone is administered for 5–8 days; followed by the administering of the same dosage of estrogen and a progestogen corresponding in progestogenic activity to 0.25–1.0 mg of norethindrone for 7–11 days; followed by the administering of the same dosage of estrogen and a progestogen corresponding in progestogenic activity to 0.35–2.0 mg of norethindrone for 3–7 days; followed by 6–8 days without administering either an estrogen or a progestogen.

10 Claims, No Drawings

TRIPHASIC ORAL CONTRACEPTIVE

This is a continuation-in-part of application Ser. No. 536,135, filed Sept. 26, 1983.

This invention relates to a method of effecting contraception in the human female. More particularly, this invention relates to a method of effecting contraception comprising the oral administration of a low but contraceptively effective daily dosage of a combination of an estrogen and a progestogen for 21 successive days.

Oral contraceptives first became available in the early 1960's. Since that time, a number of regimens for controlling ovulation and conception by the administration of hormones have become known and are readily available. The oral administration of combination type preparations containing both an estrogen and a progestogen has been known for some time. Some of these regimens are based upon consistent dosage of either an estrogen or progestogen or both throughout the period of administration while others are directed to regimens wherein the amount of estrogen or progestogen or both is increased or decreased during the menstrual cycle.

One disadvantage inherent in the administration of the aforementioned pure and modified sequential products involving the administration of relatively high doses of estrogen, in addition to the usual symptoms due to excessive estrogen, i.e., gastrointestinal disturbances, nausea, weight gain with formation of edema, etc., is an increase in the risk of thromboembolic disease. Many of these disadvantages can be avoided by the administration of two-stage or biphasic combination contraceptives, but even in the biphasic products it would be desirable if the ability to control the cycle could be improved.

The administration of three-stage or triphasic combination type oral contraceptives is also known. Triphasic combinations of various types are described in U.S. Pat. Nos. 4,390,531; 4,066,757; 3,957,982; 3,795,734; and 2,431,704.

In recent years data collected on the use of various oral contraceptive regimens have indicated that increased blood pressure and decreased glucose tolerance are associated with the progestogen content or progestational activity of oral contraceptives. In addition, the progestogen activity is associated with a decrease in serum high density lipoprotein values. These findings have prompted a greater emphasis on a reduction of the progestogen dosage in oral contraceptives.

There is a need, therefore, for a combination type contraceptive which contains low concentrations of estrogen and progestogen but is still effective for the prevention of pregnancy.

By the present invention a triphasic oral contraceptive regimen is provided wherein the estrogen dosage is kept constant throughout the 21-day cycle while the progestogen dosage is gradually increased in successive doses. The purpose of the invention is to lower total monthly steroid dose in the oral contraceptive while still obtaining equivalent bleeding patterns and protection against pregnancy as found with conventional oral contraceptives.

According to the present invention, reliable contraception is achieved by administering for 21 successive days to a female a combination of an estrogen and a progestogen, for the first 5–8 days in a contraceptively effective daily dosage a progestogen equivalent in effect to about 0.065–0.75 mg of norethindrone in combination an estrogen equivalent in effect to about 0.02–0.05 mg of ethinyl estradiol; followed by the administration for 7–11 days, of a daily dosage of a progestogen equivalent in effect to about 0.25–1.0 mg of a norethindrone together with an estrogen equivalent in effect to about 0.02–0.50 mg of ethinyl estradiol; and followed by the administration for 3–7 days of a daily dosage of a progestogen equivalent in effect to about 0.35–2.0 mg of norethindrone in combination an estrogen equivalent in effect to about 0.02–0.05 mg of ethinyl estradiol, provided that the dosage of estrogen is kept constant in each phase during the 21-day cycle. The actual weight amount of the dosage at each dosage level will depend upon the estrogenic and progestogenic activity, respectively, of the components selected for the dosage units.

The total number of days during which the progestogen and estrogen combinations are administered daily is 21. These are followed by 6–8 days which are free of hormone administration to approximate the natural 28-day menstrual cycle of the female. Day one of the cycle is defined as the first day of menstruation and the days are numbered sequentially thereafter until menstruation occurs again. The cycle usually lasts 28 days but it may be slightly longer or shorter. In actual practice a placebo or any other hormone-free agent such as, for example, iron supplements, may be administered during this period. Thus, in a preferred regimen, phase one would commence sometime between day 4 and day 6 of the menstrual cycle and last 5–8 days but preferably 7 days, phase two would last 7–11 days, preferably 7 days, while phase three would last 3 to 7 days, preferably 7 days.

The contraceptive composition employed in the present invention comprises 21 separate daily dosage units which are adapted for successive daily oral ingestion. The composition consists essentially of, as the first phase, 5–8 dosage units containing, in admixture with a pharmaceutically acceptable carrier, a combination of an estrogen in combination with a progestogen, followed by, as the second phase, 7–11 dosage units containing, a combination of an estrogen and a progestogen, followed by, as the third phase, 3–7 dosage units containing a combination of an estrogen and a progestogen followed by 6–8 dosage units free of estrogen and progestogen. The estrogen daily dosage is kept constant in all three phases.

Any conventional estrogen may be employed as a suitable component in the contraceptive regimen of this invention. The particular regimen employed in a daily dosage should be equal in contraceptive activity in each phase to a daily dosage of about 0.020–0.050 mg of 17α-ethinylestradiol. The preferred dosage is one equal to a daily dosage of about 0.035 mg of 17α-ethinylestradiol.

In addition to 17α-ethinylestradiol, esters and ethers of 17α-ethinylestradiol may also be employed as the estrogen component. Natural estrogens such as estrone, estradiol and estriol, and their esters, as well as the synthetic estrogens, may also be employed. The preferred estrogen is 17α-ethinylestradiol.

As the progestogen component, any progestationally active compound may be employed. The progestogen is preferably administered in a daily dosage in the first phase corresponding in progestogenic activity to 0.065–0.75 mg of norethindrone per day, during the next phase a daily dosage corresponding in progestogenic activity to 0.25–1.0 mg of norethindrone per day and during the third phase a daily dosage corresponding

in progestogenic activity to 0.35–2.0 mg of norethindrone per day.

Progestogens which may be employed as a component in the present invention include progesterone and its derivatives such as, for example, 17-hydroxyprogesterone esters and 19-nor-17-hydroxyprogesterone esters, 17α-ethinyltestosterone, 17α-ethinyl-19-nortestosterone and derivatives thereof, norethindrone, and D-17β-acetoxy-13β-ethyl-17α-ethinyl-gon-4-en-3-one oxime. The preferred progestogens are norethindrone, D-norgestrel and D-17β-acetoxy-13β-ethyl-17α-ethinyl-gon-4-en-3-one oxime (norgestimate).

The estrogen and progestogen components are preferably administered together orally in a pharmaceutically acceptable nontoxic carrier, but they can also be administered separately or parenterally. In general, the effective agents are processed, together with the usual additives, vehicles and/or flavor-ameliorating agents normally employed in Galenic pharmacy, in accordance with generally accepted pharmaceutical practices. For the preferred oral administration, tablets, dragees, capsules, pills, suspensions or solutions are particularly suitable; for parenteral application, oily solutions such as, for example, sesame oil or castor oil solutions which can optionally additionally contain a diluent such as, for example, benzyl benzoate or benzyl alcohol.

In the case of the preferred oral application, the three-phase combination-type contraceptives are preferably packaged in the form of a pharmaceutical kit or package in which the daily dosages are arranged for proper sequential administration. This invention also relates, therefore, to a pharmaceutical unit which contains combination-type contraceptives in 28 dosage units in a synchronized, fixed sequence, wherein the sequence or arrangement of the dosage units corresponds to the stages of daily administration.

The pharmaceutical unit can be, e.g., in the form of a transparent package having 28 dosage units arranged sequentially and consisting of 7 tablets for the first phase, followed by 7 tablets for the second phase, followed by 7 tablets for the third phase, and finally followed by 7 placebos. A single tablet is to be taken each day over a period of 28 days.

Without further elaboration it is believed that one skilled in the art, using the preceding description, can fully utilize the present invention. The following preferred specific embodiments are to be construed as merely illustrative of the invention and are not meant to limit the invention in any way.

EXAMPLE 1

Composition of a tablet for each stage:

1st Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.50 mg.	norethindrone
88.9 mg.	lactose anhydrous DT
10.0 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
199.935 mg.	total weight
2nd Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.75 mg.	norethindrone
88.70 mg.	lactose anhydrous DT
10.02 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
100.005 mg.	total weight
3rd Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
1.0 mg.	norethindrone
88.5 mg.	lactose anhydrous DT
10.0 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
100.035 mg.	total weight

EXAMPLE 2

Composition of a tablet for each stage:

1st Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.50 mg.	D-17β-acetoxy-13β-ethyl-17α-ethinyl-gon-4-en-3-one oxime
87.9 mg.	lactose anhydrous DT
11.1 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
100.035 mg.	total weight
2nd Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.75 mg.	D-17β-acetoxy-13β-ethyl-17α-ethinyl-gon-4-en-3-one oxime
89.70 mg.	lactose anhydrous DT
9.02 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
100.005 mg.	total weight
3rd Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
1.0 mg.	D-17β-acetoxy-13β-ethyl-17α-ethinyl-gon-4-en-3-one oxime
87.5 mg.	lactose anhydrous DT
11.0 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
100.035 mg.	total weight

EXAMPLE 3

Composition of a tablet for each stage:

1st Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.50 mg.	D-norgestrel
90.0 mg.	lactose anhydrous DT
9.0 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
100.035 mg.	total weight
2nd Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.75 mg.	D-norgestrel
87.70 mg.	lactose anhydrous DT
11.02 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
100.005 mg.	total weight
3rd Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
1.0 mg.	D-norgestrel
89.5 mg.	lactose anhydrous DT
9.0 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
100.035 mg.	total weight

EXAMPLE 4

Composition of a tablet for each stage:

1st Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.180 mg.	norgestimate
90.200 mg.	lactose anhydrous DT

-continued

9.085 mg.	pregelatinized starch N.F.
0.500 mg.	magnesium stearate N.F.
100.000 mg.	total weight
	2nd Stage 7 Tablets
0.035 mg.	17α-ethinylestradiol
0.215 mg.	norgestimate
90.150 mg.	lactose anhydrous DT
9.100 mg.	pregelatinized starch N.F.
0.500 mg.	magnesium stearate N.F.
100.000 mg.	total weight
	3rd Stage 7 Tablets
0.035 mg.	17α-ethinylestradiol
0.250 mg.	norgestimate
90.115 mg.	lactose anhydrous DT
9.100 mg.	pregelatinized starch N.F.
0.500 mg.	magnesium stearate N.F.
100.000 mg.	total weight

EXAMPLE 5

Composition of a tablet for each stage:

	1st Stage 7 Tablets
0.035 mg.	17α-ethinylestradiol
0.250 mg.	norethindrone
88.9 mg.	lactose anhydrous DT
10.32 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
100.006 mg.	total weight
	2nd Stage 7 Tablets
0.035 mg.	17α-ethinylestradiol
0.375 mg.	norethindrone
88.70 mg.	lactose anhydrous DT
10.39 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
100.000 mg.	total weight
	3rd Stage 7 Tablets
0.035 mg.	17α-ethinylestradiol
0.500 mg.	norethindrone
88.5 mg.	lactose anhydrous DT
10.47 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
100.005 mg.	total weight

EXAMPLE 6

Composition of a tablet for each stage:

	1st Stage 7 Tablets
0.035 mg.	17α-ethinylestradiol
0.05 mg.	D-norgestrel
90.0 mg.	lactose anhydrous DT
9.43 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
100.015 mg.	total weight
	2nd Stage 7 Tablets
0.035 mg.	17α-ethinylestradiol
0.075 mg.	D-norgestrel
87.70 mg.	lactose anhydrous DT
11.69 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
100.000 mg.	total weight
	3rd Stage 7 Tablets
0.035 mg.	17α-ethinylestradiol
0.100 mg.	D-norgestrel
89.3 mg.	lactose anhydrous DT
9.88 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
100.015 mg.	total weight

EXAMPLE 7

Composition of a tablet for each stage:

	1st Stage 7 Tablets
0.035 mg.	17α-ethinylestradiol
0.025 mg.	D-norgestrel
90.00 mg.	lactose anhydrous DT
9.45 mg.	pregelatinized starch N.F.
0.50 mg.	magnesium stearate N.F.
100.000 mg.	total weight
	2nd Stage 7 Tablets
0.035 mg.	17α-ethinylestradiol
0.038 mg.	D-norgestrel
87.70 mg.	lactose anhydrous DT
11.74 mg.	pregelatinized starch N.F.
0.50 mg.	magnesium stearate N.F.
100.013 mg.	total weight
	3rd Stage 7 Tablets
0.035 mg.	17α-ethinylestradiol
0.050 mg.	d-norgestrel
89.500 mg.	lactose anhydrous DT
9.93 mg.	pregelatinized starch N.F.
0.50 mg.	magnesium stearate N.F.
100.015 mg.	total weight

EXAMPLE 8

Composition of a tablet for each stage:

	1st Stage 7 Tablets
0.035 mg.	17α-ethinylestradiol
0.090 mg.	norgestimate
90.200 mg.	lactose anhydrous DT
9.18 mg.	pregelatinized starch N.F.
0.50 mg.	magnesium stearate N.F.
100.005 mg.	total weight
	2nd Stage 7 Tablets
0.035 mg.	17α-ethinylestradiol
0.100 mg.	norgestimate
90.150 mg.	lactose anhydrous DT
9.23 mg.	pregelatinized starch N.F.
0.50 mg.	magnesium stearate N.F.
100.015 mg.	total weight
	3rd Stage 7 Tablets
0.035 mg.	17α-ethinylestradiol
0.125 mg.	norgestimate
90.115 mg.	lactose anhydrous DT
9.230 mg.	pregelatinized starch N.F.
0.500 mg.	magnesium stearate N.F.
100.005 mg.	total weight

Clinical Tests

EXAMPLE 9

A preparation according to Example 1 was administered in three separate studies to a total of 656 women of child-bearing age. Subjects meeting the selection criteria were administered the contraceptive formulation on a regimen of 21 days on medication and 7 days off for up to 12 cycles.

The preparation was shown to be highly efficacious in preventing pregnancy. In each study the bleeding pattern consistently showed a decrease in the incidence of midcycle breakthrough bleeding and/or spotting.

Having described the invention in specific detail and exemplified the manner in which it may be carried into practice, it will be apparent to those skilled in the art that innumerable variations, applications, modifications, and extensions of the basic principles involved may be made without departing from its spirit or scope. It is to

be understood that the foregoing is merely exemplary and the present invention is not to be limited to the specific form or arrangements of parts herein described and shown.

I claim:

1. A method of contraception which comprises administering for 21 successive days to a female of childbearing age a combination of an estrogen and a progestogen in a jointly contraceptively effective daily dosage corresponding in estrogenic activity to 0.02–0.05 mg of 17α-ethinylestradiol and in progestogenic activity to 0.[illegible]–0.75 mg of norethindrone for 5–8 days; for the next 7[illegible] days an estrogen daily dosage equal to 0.02–0.[illegible]mg of 17α-ethinylestradiol and in progestogenic activity to 0.250–1.0 mg of norethindrone; and for the next 3–7 days an estrogen daily dosage equal to 0.02–0.[illegible]mg of 17α-ethinylestradiol and in progestogenic activity 0.35–2.0 mg of norethindrone; followed by 6–8 days without estrogen and progestogen administration, provided that the estrogen daily dosage is the same for each period.

2. The method of claim 1 wherein the estrogen and progestogen are administered orally and the period specified in each phase is seven days.

3. The method of claim 2 wherein the estrogen and progestogen are administered in admixture.

4. The method of claim 1 wherein the progestogen is selected from D-norgestrel, norethindrone, progesterone and D-17β-acetoxy-13β-ethyl-17α-ethinyl-gon-4-en-3-one oxime.

5. The method of claim 3 wherein the estrogen is selected from 17α-ethinylestradiol, estrone, estradiol and estriol.

6. The method of claim 3 wherein the estrogen is 17α-ethinylestradiol and the progestogen is norethindrone

7. The method of claim 1 wherein the estrogen is 17α-ethinylestradiol and the progestogen is D-17β-acetoxy-13β-ethyl-17α-ethinyl-gon-4-en-3-one oxime.

8. The method of claim 6 wherein the estrogen daily dosage is 0.035 mg for each 7 day period and the progestogen daily dosage is 0.5 mg for the first 7 days, 0.75 mg for the second 7 days and 1.0 mg for the third 7 days.

9. The contraception method of claim 1 which comprises administering for 21 successive days to a female of childbearing age a combination of 17α-ethinylestradiol and norethindrone in a contraceptively effective daily dosage corresponding to 0.035 mg of 17α-ethinylestradiol and 0.50 mg of norethindrone for 7 days; for the next 7 days a daily dosage equal to 0.035 mg of 17α-ethinylestradiol and 0.75 mg of norethindrone; and for the next 7 days a daily dosage equal to 0.035 mg of 17α-ethinylestradiol and 1.0 mg of norethindrone; followed by 7 days without estrogen and progestogen administration.

10. The contraception method of claim 1 which comprises administering for 21 successive days to a female of childbearing age a combination of 17α-ethinylestradiol and norgestimate in a contraceptively effective daily dosage corresponding to 0.035 mg of 17α-ethinylestradiol and 0.180 mg of norgestimate for 7 days; for the next 7 days a daily dosage equal to 0.035 mg of 17α-ethinylestradiol and 0.215 mg of norgestimate; and for the next 7 days a daily dosage equal to 0.035 mg of 17α-ethinylestradiol and 0.250 mg of norgestimate; followed by 7 days without estrogen and progestogen administration.

* * * * *

Exhibit C

FIP9012 OR 4,616,006

United States Patent [19]

Pasquale

[11] **Patent Number: 4,616,006**

[45] **Date of Patent: Oct. 7, 1986**

[54] **TRIPHASIC ORAL CONTRACEPTIVE**

[75] Inventor: **Samuel A. Pasquale, Basking Ridge, N.J.**

[73] Assignee: **Ortho Pharmaceutical Corporation, Raritan, N.J.**

[21] Appl. No.: **744,189**

[22] Filed: **Jun. 13, 1985**

Related U.S. Application Data

[63] Continuation of Ser. No. 607,038, May 4, 1984, Pat. No. 4,544,554, which is a continuation-in-part of Ser. No. 536,135, Sep. 26, 1983, abandoned.

[51] Int. Cl.[4] A01N 45/00; A61K 31/56

[52] U.S. Cl. 514/170

[58] Field of Search 514/170

[56] **References Cited**

U.S. PATENT DOCUMENTS

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4,544,554 10/1985 Pasquale 514/170

Primary Examiner—Elbert L. Roberts

Attorney, Agent, or Firm—Benjamin F. Lambert

[57] **ABSTRACT**

A method of contraception in which an estrogen and a progestogen are administered daily in a three phase sequence for 21 days is disclosed. In the first phase a combination of an estrogen and a progestogen in a low but contraceptively effective daily dosage corresponding in estrogenic activity to 0.02–0.05 mg of 17α-ethinylestradiol and in progestogenic activity to 0.065–0.75 mg of norethindrone is administered for 5–8 days; followed by the administering of the same dosage of estrogen and a progestogen corresponding in progestogenic activity to 0.25–1.0 mg of norethindrone for 7–11 days; followed by the administering of the same dosage of estrogen and a progestogen corresponding in progestogenic activity to 0.35–2.0 mg of norethindrone for 3–7 days; followed by 6–8 days without administering either an estrogen or a progestogen.

10 Claims, No Drawings

TRIPHASIC ORAL CONTRACEPTIVE

This is a continuation of application Ser. No. 607,038, filed May 4, 1984, now U.S. Pat. No. 4,544,554, which in turn is a continuation-in-part of application Ser. No. 536,135, filed Sept. 26, 1983, now abandoned.

This invention relates to a method of effecting contraception in the human female. More particularly, this invention relates to a method of effecting contraception comprising the oral administration of a low but contraceptively effective daily dosage of a combination of an estrogen and a progestogen for 21 successive days.

Oral contraceptives first became available in the early 1960's. Since that time, a number of regimens for controlling ovulation and conception by the administration of hormones have become known and are readily available. The oral administration of combination type preparations containing both an estrogen and a progestogen has been known for some time. Some of these regimens are based upon consistent dosage of either an estrogen or progestogen or both throughout the period of administration while others are directed to regimens wherein the amount of estrogen or progestogen or both is increased or decreased during the menstrual cycle.

One disadvantage inherent in the administration of the aforementioned pure and modified sequential products involving the administration of relatively high doses of estrogen, in addition to the usual symptoms due to excessive estrogen, i.e., gastrointestinal disturbances, nausea, weight gain with formation of edema, etc., is an increase in the risk of thromboembolic disease. Many of these disadvantages can be avoided by the administration of two-stage or biphasic combination contraceptives, but even in the biphasic products it would be desirable if the ability to control the cycle could be improved.

The administration of three-stage or triphasic combination type oral contraceptives is also known. Triphasic combinations of various types are described in U.S. Pat. Nos. 4,390,531; 4,066,757; 3,957,982; 3,795,734; and 2,431,704.

In recent years data collected on the use of various oral contraceptive regimens have indicated that increased blood pressure and decreased glucose tolerance are associated with the progestogen content or progestational activity of oral contraceptives. In addition, the progestogen activity is associated with a decrease in serum high density lipoprotein values. These findings have prompted a greater emphasis on a reduction of the progestogen dosage in oral contraceptives.

There is a need, therefore, for a combination type contraceptive which contains low concentrations of estrogen and progestogen but is still effective for the prevention of pregnancy.

By the present invention a triphasic oral contraceptive regimen is provided wherein the estrogen dosage is kept constant throughout the 21-day cycle while the progestogen dosage is gradually increased in successive doses. The purpose of the invention is to lower total monthly steroid dose in the oral contraceptive while still obtaining equivalent bleeding patterns and protection against pregnancy as found with conventional oral contraceptives.

According to the present invention, reliable contraception is achieved by administering for 21 successive days to a female a combination of an estrogen and a progestogen, for the first 5–8 days in a contraceptively effective daily dosage a progestogen equivalent in effect to about 0.065–0.75 mg of norethindrone in combination an estrogen equivalent in effect to about 0.02–0.05 mg of ethinyl estradiol; followed by the administration for 7–11 days, of a daily dosage of a progestogen equivalent in effect to about 0.25–1.0 mg of a norethindrone together with an estrogen equivalent in effect to about 0.02–0.50 mg of ethinyl estradiol; and followed by the administration for 3–7 days of a daily dosage of a progestogen equivalent in effect to about 0.35–2.0 mg of norethindrone in combination an estrogen equivalent in effect to about 0.02–0.05 mg of ethinyl estradiol, provided that the dosage of estrogen is kept constant in each phase during the 21-day cycle. The actual weight amount of the dosage at each dosage level will depend upon the estrogenic and progestogenic activity, respectively, of the components selected for the dosage units.

The total number of days during which the progestogen and estrogen combinations are administered daily is 21. These are followed by 6–8 days which are free of hormone administration to approximate the natural 28-day menstrual cycle of the female. Day one of the cycle is defined as the first day of menstruation and the days are numbered sequentially thereafter until menstruation occurs again. The cycle usually lasts 28 days but it may be sliightly longer or shorter. In actual practice a placebo or any other hormone-free agent such as, for example, iron supplements, may be administered during this period. Thus, in a preferred regimen, phase one would commence sometime between day 4 and day 6 of the menstrual cycle and last 5–8 days but preferably 7 days, phase two would last 7–11 days, preferably 7 days, while phase three would last 3 to 7 days, preferably 7 days.

The contraceptive composition employed in the present invention comprises 21 separate daily dosage units which are adapted for successive daily oral ingestion. The composition consists essentially of, as the first phase, 5–8 dosage units containing, in admixture with a pharmaceutically acceptable carrier, a combination of an estrogen in combination with a progestogen, followed by, as the second phase, 7–11 dosage units containing, a combination of an estrogen and a progestogen, followed by, as the third phase, 3–7 dosage units containing a combination of an estrogen and a progestogen followed by 6–8 dosage units free of estrogen and progestogen. The estrogen daily dosage is kept constant in all three phases.

Any conventional estrogen may be employed as a suitable component in the contraceptive regimen of this invention. The particular regimen employed in a daily dosage should be equal in contraceptive activity in each phase to a daily dosage of about 0.020–0.050 mg of 17α-ethinylestradiol. The preferred dosage is one equal to a daily dosage of about 0.035 mg of 17α-ethinylestradiol.

In addition to 17α-ethinylestradiol, esters and ethers of 17α-ethinylestradiol may also be employed as the estrogen component. Natural estrogens such as estrone, estradiol and estriol, and their esters, as well as the synthetic estrogens, may also be employed. The preferred estrogen is 17α-ethinylestradiol.

As the progestogen component, any progestationally active compound may be employed. The progestogen is preferably administered in a daily dosage in the first phase corresponding in progestogenic activity to 0.065–0.75 mg of norethindrone per day, during the next phase a daily dosage corresponding in progesto-

genic activity to 0.25–1.0 mg of norethindrone per day and during the third phase a daily dosage corresponding in progestogenic activity to 0.35–2.0 mg of norethindrone per day.

Progestogens which may be employed as a component in the present invention include progesterone and its derivatives such as, for example, 17-hydroxyprogesterone esters and 19-nor-17-hydroxyprogesterone esters, 17α-ethinyltestosterone, 17α-ethinyl-19-nortestosterone and derivatives thereof, norethindrone, and D-17β-acetoxy-13β-ethyl-17α-ethinyl-gon-4-en-3-one oxime. The preferred progestogens are norethindrone, D-norgestrel and D-17β-acetoxy-13β-ethyl-17α-ethinyl-gon-4-en-3-one oxime (norgestimate).

The estrogen and progestogen components are preferably administered together orally in a pharmaceutically acceptable nontoxic carrier, but they can also be administered separately or parenterally. In general, the effective agents are processed, together with the usual additives, vehicles and/or flavor-ameliorating agents normally employed in Galenic pharmacy, in accordance with generally accepted pharmaceutical practices. For the preferred oral administration, tablets, dragees, capsules, pills, suspensions or solutions are particularly suitable; for parenteral application, oily solutions such as, for example, sesame oil or castor oil solutions which can optionally additionally contain a diluent such as, for example, benzyl benzoate or benzyl alcohol.

In the case of the preferred oral application, the three-phase combination-type contraceptives are preferably packaged in the form of a pharmaceutical kit or package in which the daily dosages are arranged for proper sequential administration. This invention also relates, therefore, to a pharmaceutical unit which contains combination-type contraceptives in 28 dosage units in a synchronized, fixed sequence, wherein the sequence or arrangement of the dosage units corresponds to the stages of daily administration.

The pharmaceutical unit can be, e.g., in the form of a transparent package having 28 dosage units arranged sequentially and consisting of 7 tablets for the first phase, followed by 7 tablets for the second phase, followed by 7 tablets for the third phase, and finally followed by 7 placebos. A single tablet is to be taken each day over a period of 28 days.

Without further elaboration it is believed that one skilled in the art, using the preceding description, can fully utilize the present invention. The following preferred specific embodiments are to be construed as merely illustrative of the invention and are not meant to limit the invention in any way.

EXAMPLE 1

Composition of a tablet for each stage:

1st Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.50 mg.	norethindrone
88.9 mg.	lactose anhydrous DT
10.0 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
99.935 mg.	total weight

2nd Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.75 mg.	norethindrone
88.70 mg.	lactose anhydrous DT
10.02 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
100.05 mg.	total weight

3rd Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
1.0 mg.	norethindrone
88.5 mg.	lactose anhydrous DT
10.0 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
100.035 mg.	total weight

EXAMPLE 2

Composition of a tablet for each stage:

1st Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.50 mg.	D-17β-acetoxy-13β-ethyl-17α-ethinyl-gon-4-en-3-one oxime
87.9 mg.	lactose anhydrous DT
11 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
100.035 mg.	total weight

2nd Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.75 mg.	D-17β-acetoxy-13β-ethyl-17α-ethinyl-gon-4-en-3-one oxime
89.70 mg.	lactose anhydrous DT
9.02 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
100.005 mg.	total weight

3rd Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
1.0 mg.	D-17β-acetoxy-13β-ethyl-17α-ethinyl-gon-4-en-3-one oxime
87.5 mg.	lactose anhydrous DT
11.0 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
100.035 mg.	total weight

EXAMPLE 3

Composition of a tablet for each stage:

1st Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.50 mg.	D-norgestrel
90.0 mg.	lactose anhydrous DT
9.0 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
100.035 mg.	total weight

2nd Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.75 mg.	D-norgestrel
87.70 mg.	lactose anhydrous DT
11.02 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
100.005 mg.	total weight

3rd Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
1.0 mg.	D-norgestrel
89.5 mg.	lactose anhydrous DT
9.0 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
100.035 mg.	total weight

EXAMPLE 4

Composition of a tablet for each stage:

1st Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.180 mg.	norgestimate
90.200 mg.	lactose anhydrous DT
9.085 mg.	pregelatinized starch N.F.
0.500 mg.	magnesium stearate N.F.
100.000 mg.	total weight

2nd Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.215 mg.	norgestimate
90.150 mg.	lactose anhydrous DT
9.100 mg.	pregelatinized starch N.F.
0.500 mg.	magnesium stearate N.F.
100.000 mg.	total weight

3rd Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.250 mg.	norgestimate
90.115 mg.	lactose anhydrous DT
9.100 mg.	pregelatinized starch N.F.
0.500 mg.	magnesium stearate N.F.
100.000 mg.	total weight

EXAMPLE 5

Composition of a tablet for each stage:

1st Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.250 mg.	norethindrone
88.9 mg.	lactose anhydrous DT
10.32 mg.	pregelatinized starch N.F
0.5 mg.	magnesium stearate N.F.
100.006 mg.	total weight

2nd Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.375 mg.	norethindrone
88.70 mg.	lactose anhydrous DT

-continued

2nd Stage 7 Tablets	
10.39 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
100.000 mg.	total weight

3rd Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.500 mg.	norethindrone
88.5 mg.	lactose anhydrous DT
10.47 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
100.005 mg.	total weight

EXAMPLE 6

Composition of a tablet for each stage:

1st Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.05 mg.	D-norgestrel
90.0 mg.	lactose anhydrous DT
9.43 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
100.015 mg.	total weight

2nd Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.075 mg.	D-norgestrel
87.70 mg.	lactose anhydrous DT
11.69 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
100.005 mg.	total weight

3rd Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.100 mg.	D-norgestrel
89.5 mg.	lactose anhydrous DT
9.88 mg.	pregelatinized starch N.F.
0.5 mg.	magnesium stearate N.F.
100.015 mg.	total weight

EXAMPLE 7

Composition of a tablet for each stage:

1st Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.025 mg.	D-norgestrel
90.00 mg.	lactose anhydrous DT
9.45 mg.	pregelatinized starch N.F.
0.50 mg.	magnesium stearate N.F.
100.000 mg.	total weight

2nd Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.038 mg.	D-norgestrel
87.70 mg.	lactose anhydrous DT
11.74 mg.	pregelatinized starch N.F.
0.50 mg.	magnesium stearate N.F.

-continued

2nd Stage 7 Tablets	
100.013 mg.	total weight

3rd Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.050 mg.	D-norgestrel
89.500 mg.	lactose anhydrous DT
9.93 mg.	pregelatinized starch N.F.
0.50 mg.	magnesium stearate N.F.
100.015 mg.	total weight

EXAMPLE 8

Composition of a tablet for each stage:

1st Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.090 mg.	norgestimate
90.200 mg.	lactose anhydrous DT
9.18 mg.	pregelatinized starch N.F.
0.50 mg.	magnesium stearate N.F.
100.005 mg.	total weight

2nd Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.100 mg.	norgestimate
90.150 mg.	lactose anhydrous DT
9.23 mg.	pregelatinized starch N.F.
0.50 mg.	magnesium stearate N.F.
100.015 mg.	total weight

3rd Stage 7 Tablets	
0.035 mg.	17α-ethinylestradiol
0.125 mg.	norgestimate
90.115 mg.	lactose anhydrous DT
9.230 mg.	pregelatinized starch N.F.
0.500 mg.	magnesium stearate N.F.
100.005 mg.	total weight

Clinical Tests

EXAMPLE 9

A preparation according to Example 1 was administered in three separate studies to a total of 656 women of child-bearing age. Subjects meeting the selection criteria were administered the contraceptive formulation on a regimen of 21 days on medication and 7 days off for up to 12 cycles.

The preparation was shown to be highly efficacious in preventing pregnancy. In each study the bleeding pattern consistently showed a decrease in the incidence of midcycle breakthrough bleeding and/or spotting.

Having described the invention in specific detail and exemplified the manner in which it may be carried into practice, it will be apparent to those skilled in the art that innumerable variations, applications, modifications, and extensions of the basic principles involved may be made without departing from its spirit or scope. It is to be understood that the foregoing is merely exemplary and the present invention is not to be limited to the specific form or arrangements of parts herein described and shown.

I claim:

1. A triphasic oral contraceptive unit consisting of 21 separate dosage units, adapted for successive daily oral administration comprising:

7 dosage units containing, in admixture with a pharmaceutically acceptable carrier, a combination of an estrogen and a progestogen at contraceptively effective dosages corresponding in activity to 0.02–0.05 mg of 17α-ethinylestradiol and in progestogenic activity to 0.065–0.75 mg of norethindrone as the first phase; followed by 7 dosage units containing in admixture with a pharmaceutically acceptable carrier, a combination of an estrogen at a contraceptively effective dosage corresponding in activity to 0.02–0.05 mg of 17α-ethinylestradiol and in progestogenic activity to 0.25–1.0 mg of norethindrone as the second phase; followed by 7 dosage units containing in admixture with a pharmaceutically acceptable carrier, a combination of an estrogen at a contraceptively effective dosage corresponding to 0.02–0.05 mg of 17α-ethinylestradiol and in progestogenic activity to 0.35–2.0 mg of norethindrone as the third phase, and optionally containing 7 dosage units free of estrogen and progestogen; provided that the estrogen daily dosage is the same in all three phases.

2. The unit according to claim 1 wherein the dosage units are in the form of tablets.

3. The unit according to claim 1 wherein the estrogen is selected from 17α-ethinylestradiol, estrone, estradiol and estriol.

4. The unit according to claim 2 wherein the estrogen is 17α-ethinylestradiol.

5. The unit according to claim 1 wherein the progestogen is selected from D-norgestrel, norethindrone, progesterone and D-17β-acetoxy-13β-ethyl-17α-ethinyl-gon-4-en-3-one oxime.

6. The unit according to claim 5 wherein the progestogen is norethindrone.

7. The unit according to claim 5 wherein the progestogen is D-17β-acetoxy-13β-ethyl-17α-ethinyl-gon-4-en-3-one oxime.

8. A composition according to claim 1 wherein the estrogen daily dosage in all three phases is equivalent to 0.035 mg of 17α-ethinylestradiol; and the progestogen daily dosage is equivalent to 0.50 mg of norethindrone in the first phase, 0.75 mg of norethindrone in the second phase and 1.0 mg of norethindrone in the third phase.

9. A composition according to claim 1 wherein the estrogen daily dosage in all three phases is equivalent to 0.035 mg of 17α-ethinylestradiol; and the progestogen daily dosage is equivalent to 0.180 mg of norgestimate in the first phase, 0.215 mg of norgestimate in the second phase and 0.250 mg of norgestimate in the third phase.

10. A triphasic oral contraceptive unit consisting of 21 separate dosage units, adapted for successive daily oral administration comprising:

5–8 dosage units containing, in admixture with a pharmaceutically acceptable carrier, a combination of an estrogen and a progestogen at contraceptively effective dosages corresponding in activity to 0.02–0.05 mg of 17α-ethinylestradiol and in progestogenic activity to 0.065–0.75 mg of norethindrone as the first phase; followed by 7–11 dosage