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Attorneys for plaintiff Ortho-McNeil Pharmaceutical, Inc.

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UNITED STATES DISTRICT COURT FOR THE DISTRICT OF NEW JERSEY

ORTHO-MeNEIL PHARMACEU INC., Route 202	TICAL,)))			
Raritan, NJ 08869)			
Plaintiff,)))	Civil Action No.	<u>oo-</u>	_280
vs.	į			
BARR LABORATORIES, INC. 2 Quaker Road)))	DISIG	2008 JUN	#ILLIAM
Pomona, NY 10970 Defendant.)))	RICT C	₹ -9	TYM T
	<u>COMPLAINT</u>	ATES OURT	LS:1 d	D SH, CLERK

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).

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- 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.

<u>COUNT I</u>

(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. (Λ copy of the '839 patent is attached hereto as Exhibit Λ).
- 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;
 - 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.

Dated: June **9**, 2000

Respectfully submitted,

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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 Naboratories, Inc., Civil Action No. 99-CV-235 (GEB), is pending before the Hon. Garrett E. Brown, Jr.

William J. Brennan III

United States Patent [19] Patent Number: [11] 4,530,839 Pasquale Date of Patent: [45] Jul. 23, 1985 [54] TRIPHASIC ORAL CONTRACEPITVE 4378.356 3/1913 De Jager _ [75] Inventor: Samuel A. Pasquale, Basking Ridge, Primary Exeminer-Elbert L. Roberts Attorney, Agent, or Firm-Benjamin F. Lambert [73] Assignee: Ortho Pharmaceutical Corporation, Raritan, NJ. ABSTRACT A method of contraception in which an estrogen and a [21] Appl. No.: 536,135 progressoges are administered daily for 21 days, the first [22] Filed: Sep. 26, 1983 seven days at a low contraceptively effective daily dosc, Int. CL³ A01N 45/00 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 [52] U.S. Cl. 514/171; 514/843 [58] Field of Search 424/238, 241, 239 daily progessogen dose of 2-2.5 times that of the first 7 days, provided that the dosage of the enrogen is main-[56] References Cited tained at a commant level for the entire 21 days. U.S. PATENT DOCUMENTS 4.291.028 9/1981 Vorys 424/23E 9 Claims, No Drawings

United States Patent [19] 4,530,839 [11] Patent Number: Pasquale [45] Date of Patent: Jul. 23, 1985 [54] TRIPHASIC ORAL CONTRACEPITYE 4,378,356 3/1983 De Jager -[75] Inventor: Samuel A. Pasquale, Basking Ridge, Primary Examiner—Elbert L. Roberts Attorney, Agent, or Firm-Benjamin F. Lambert Ortho Pharmaceutical Corporation, [73] Assignee: [57] ABSTRACT Raritan, N.J. A method of contraception in which an estrogen and a [21] Appl. No.: 536,135 progestogen are administered daily for 21 days, the first [22] Filed: Sep. 26, 1983 seven days at a low contraceptively effective daily dose, the next 7 days at a daily progestogen dose about 1.5-2 [51] Int. CL³ A01N 45/00 times that of the first 7 days, and the next 7 days at a U.S. CL 514/171: 514/843 daily progestogen dose of 2-2.5 times that of the first 7 days, provided that the dosage of the estrogen is main-[56] References Cited tained at a constant level for the entire 21 days. U.S. PATENT DOCUMENTS 4,291,028 9/1981 Vorys 424/238 9 Claims, No Drawings

4,530,839

TRIPHASIC ORAL CONTRACEPTIVE

This invention relates to a method of contraception

comprising the oral administration of a low but con- 5 traceptively 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 de- 10 veloped. 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 gesta- 15 gen, 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 progesto- 20 gen 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 25 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 accept- 30 able 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 nor-

mai 28-day female cycle.

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 40 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 45 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 progestugen are administered for the first 4-6 days, and for the 50 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 55 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 60 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 65 serum high density lipoprotein values. These findings have prompted a greater emphasis on a reduction of the progestogen dosage in oral contraceptives.

2 There is a need, therefore, for a combination type contraceptive which contains low concentrations of extrogen 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 dotage is kept constant throughout the 21-day cycle while the progestogen dosage is gradually increased in succesive 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 docage units.

The total number of days during which the progestogen and extrogen 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 One disadvantage inherent in the administration of 35 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 pliase to a daily dosage of about 0.020-0.050 mg of 1/a-ethinylestradiol. The preferred dosage is one equal to a daily dosage of about 0.035 mg of 17a-ethinyles-

In addition to 17a-ethinylestradiol, esters and ethers of 17a-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 17a-ethinylestradiol.

As the progestogen component, any progestationally active compound may be employed. The progestogen is 4,530,839

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 norethin-

Progestogens which may be employed as a component in the present invention include progesterone and 10 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-scetoxy-13β-ethyl-17α-ethinyl-gon-4-en-3-one oxime. 15 The preferred progestogens are norethindrone, d-norgestrel and D-17β-scetoxy-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:

1	st Stage 7 Tablets
0.50 mg. \$8.9 mg.	17a-ethinylestradiol norethindrone lactore anhydrous DT pregalatameed starch N.F. magnetium steerate N.T.
♥1,936 eng. 2	sgaal weight a <u>d Stage 7 Tablets</u> 17g-eshinylestradini

-continued
0.75 mg. norethindrone 22.70 mg. incrose anhydrous DT 10.02 mg. pregaletanized starch N.F. 0.5 mg. magnetium stearate N.T.
100.06 mg. total weight 3rd Stage 7 Tablets
0.036 mg. 17a-ethinylmaradiol 1.0 mg. sorethindrone 83.5 mg. lactose anhydrone DT 10.0 mg. pregulationed starck N.F.
0.5 mg. magnesium stearate N.T. 100.034 mg. total weight

EXAMPLE 2

Composition of a tablet for each stage:

but Staye ? Tablets
0.036 mg. 17a-ethinylesmadiol
0.50 mg. D-17#-ecstony-13#-ethyl-17a-ethinyl-gon-t-en-
J-one gaine
at e me, lactent ankydrost DT
11.1 mg. pregulationized search N.F.
0.5 mg. magnetium menrate N.T.
100.036 mg. socal weight 2nd Scare 7 Tablets

0.036 mg. 17a-ethinylestradiol
0.75 mg. D-176-scetoxy-136-cthyl-17a-ethinyl-gon + ch-
3-one oxime
\$9.70 eng. Increase authydrona DT
e 02 mar, presalatamized starch N.F.
0.5 mg. magnesium stearate N.T.
100 CD6 mg. total weight
3rd Stage 7 Tabless
0.036 mg. 17a-rthinylestradiol
1.0 mg. D-176-accepty-139-mayer-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1
87.5 mg. lamose anhydrous DT
11.0 mg. pregalatemized starch N.F.
0.5 mg. magnessum stentate N.T.
100.036 mg. total weight

EXAMPLE 3

Composition of a tablet for each stage:

	age 7 Tablets
0.035 mg. 17o	-cibin y lextradiol
0.50 mg, d-60	-recutroi
40.0 mg, lact	me anhydrous DT
9.0 mg, p/t1	estalanted March N.F.
0.5 mg mat	nesium wearste N.T.
_1035 mg. tota	J weight
2nd 5	tage 7 Tablets
0.035 mg. 174	-critinylestradiol
0.75 mg, d-e	organitel
17.70 me. lec	war schydrow DT
11 02 AR. 1975	ealptanted starch N.F.
0.5 mg. ma	goesium stearate N.T.
100.005 mg. 104	
3rd S	Stage 7 Tablets
	o-ethinylestradici
1.0 mg. d-	apressire)
19.5 mg. lac	come ankydrosis DT
9.0 mg. nc	egalatusized starch N.F.
0.5 mg. m	agnesium sagarate N.T.
100.035 mg. 10	

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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 criteris 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 10 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.

1 claim:

1. A method of contraception which comprises ad- 25 ministering 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 17a-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 17a-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 17a-ethinylestradiol and in progestogenic activity of 0.75-2.0 mg of norethindrone; fol-

6 lowed by 7 days without estrogen and progestrogen administration, provided that the estrogen daily 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 I wherein the estrogen and progestogen are administered in admixture.

4. The method of claim I 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 17a-ethinylestradiol, estrone, estradiol

and estriol. 6. The method of claim 1 wherein the estrogen is 17a-ethinylestradial and the progestogen is norethindrone.

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

8. The method of claim 1 wherein the extrogen 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. 4.9. The contraception method of claim 1 which comprises administering for 21 successive days to a female of childbearing age a combination of 170-ethinylestradiol and norethindrone in a contraceptively effective daily dosage corresponding to 0.035 mg of 17aethinylestradiol and 0.50 mg of norethindrone for 7 days; for the next 7 days a daily dosage equal to 0.035 mg of 17a-ethinylestradiol and 0.75 mg of norethindrone; and for the next 7 days a daily dosge equal to 0.035 mg of 17a-ethinylestradiol and 1.0 mg of norethindrone; followed by 7 days without estrogen and progestogen administration.

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United States Parent [19] [11] Patent Number: Pasquale [45] Date of Patent:

4,544,554

Oct. 1, 1985

[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 17aethinylestradiol 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 extrogen or a progestogen.

10 Claims, No Drawings

[54] TRIPHASIC ORAL CONTRACEPTIVE Samuel A. Pasquale, Basking Ridge. [75] Inventor: Ortho Pharmaceutical Corporation, [73] Assigned: Raritan, NJ. The portion of the term of this patent [*] Notice: subsequent to Jul. 23, 2002 has been disclaimed. [21] Appl. No.: 607,038 May 4, 1984 [22] Filed: Related U.S. Application Data Continuation-in-part of Ser. No. 536,135, Sep. 26, 1983. [51] Int. Cl.4 A61K 31/56 [52] U.S. Cl. 514/170; 514/187; 514/177 [58] Field of Search 424/238, 241, 243 References Cited [56]

U.S. PATENT DOCUMENTS

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

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 10 an extrogen 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 avail- 15 able. 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 admin- 20 istration 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 prod- 25 ucts involving the administration of relatively high doses of estrogen, in addition to the usual symptoms due to excessive estrogen, i.e., gastrointestinal disturbances, nauses, weight gain with formation of edema, etc., is an increase in the risk of thromboembolic disease. Many of 30 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 45 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 50 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 35 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 protec- 60 ferred estrogen is 17α-ethinylestradiol. tion 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 65 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, respec-

tively, 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 menstruction 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 docage units 35 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 17a-ethinylestradiol. The preferred dotage is one equal to a daily dosage of about 0.035 mg of 17α-ethinylestradiol.

In addition to 17a-ethinylestradiol, exters and ethers of 17a-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 pre-

As the progestogen component, any progestationally active compound may be employed. The progestogen is preferably administered in a daily dotage 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 dotage corresponding 4,544,554

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 exters and 19-nor-17-hydroxyprogesterone exters, 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-10 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 45 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:

		55
	1st Stage 7 Tablets	
0.035 mg. 0.50 mg. 88.7 mg. 10.0 mg. 0.5 mg. 199.935 mg.	17s-ethiny lestradiol social indicate lactore anhydrous DT pregelatinized statch N.F. magnesium stearate N.F. total weight	66
0.035 mg. 0.75 mg. 88.70 mg. 10.02 mg. 0.5 mg. 100.03 mg.	2nd Stage 7 Tablets 17a-ethinylastradiol nornthindrone lactone anhydrous DT pregislatinism starch N.F. gasgacium starche N.F. total weight 3rd Stage 7 Tablets	6

-continued			
0.035 mg. 1.0 mg. 88.5 mg. 10.0 mg. 0.5 mg. 100.035 mg.	17e-rthinylestratiol soruthindrum: Inctose sallydrum: DT progelationed starch N.F. sugarnium sicarate N.F. total weight		

EXAMPLE 2

Composition of a tablet for each stage:

•		is Stage 7 Tablets
5	0.035 mg.	7α-ethinylestradio Σ-17β-acrinay-13β-ethyl-17α-ethinyl-gos-4-en-
	87.9 mg. 11.1 mg. 0.5 mg.	lectors ashydrous DT projektered starch N.F. magnesium steamer N.F.
0	100.033 mg.	total weight 2nd Stage 7 Tablets
	0.035 mg. 0.75 mg.	17a-ethin ylastradiol D-17 <i>B-nes</i> toxy-13 <i>B-ethyl-</i> 17a-ethinyl-gon-4-cn- 3-one oxime
:5	\$9,70 mg. 9,02 mg. 0,5 mg.	factors unbydrom DT pregelatinized starch N.F. pagnatium steamte N.F.
	100.005 mg	total weight 3rd Stage 7 Tablets
30	0.035 mg. 1.0 mg.	17g-ethinylestradiol D-17β-acetosy-13β-ethyl-17g-ethinyl-gon-4-en- 3-one ouiste
	87.5 mg. 11.0 mg. <u>0.5 mg</u> .	increase unhydrous DT progeleciationd search N.F. magnesium measure N.F.
	100,035 mg	total weight

EXAMPLE 3

Composition of a tablet for each stage:

	les Stage ? Tablem
0.035 mg.	j 7g -ctjuleytestradiol
0.50 mg	D-morgestrel
40.0 mg.	lectore askydrom DT
7.0 mg.	independ starts P.P.
0.5 mg.	magnetime stender N.F.
100.035 BL	total weight
	2nd Stage 7 Tablets
0.033 mg.	17a-ethinylestratic
0.75 mg.	D-acrestrel
\$7.70 mg.	Income anhydrous DT
11.02 mg.	communicational plants N.F.
0.5 mg	magnesimis stemrate N.F.
100,003	total weight
,	3rd Stage 7 Tableta
Q.035 mg.	17a-chinylestradio)
1.0 mg.	D-sorsexrel
17.5 mg.	lavanne ambydrowi DT
1,0 mg.	errechdeized gesch N.F.
0.5 mg	, M W
100,035 mg	

EXAMPLE 4 Composition of a tablet for each stage:

0.035 ==4	1-s Stage 7 Tables 17g-echleyisseradiol
0.190 mg. 90.200 mg.	eorgenissee lactore anhydrous DT

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-continued			F	EXAMPLE 7
9.085 mg. 0.500 mg.	pregelacinized starch N.F. magnesium steerate N.F.		Composition of a t	ablet for each stage:
100.000 mg.	total weight	5 —		
	2nd Stage 7 Tablets		_	st Stage 7 Tablets
0.035 mg .	17e-ethis ylestradiol		0.035 mg.	17e-estimylestradiol
0.215 mg.	novgastárnité		Q.025 mg.	D-sorgeried
40.130 mg.	lectore enhydrous DT		40.00 me.	lectors anhydrous DT
9.100 mg.	pregelationed starch N.F.		9.45 mg.	pregulationed starch N.F.
0. <u>500 </u> mg.	magnesium steurate N.F.	10	0.50_mg.	magazina penrate N.F.
100.000 =4.	total weight		1007000 mft.	soud weight
,	3rd Stage 7 Tablets		2	nd Stage 7 Tablets
0.035 mg.	[7a-cthinylestradio]		0.035 tog	17a-chiaylestradiol
0.250 mg.	norgentimet		0.038 mg.	D-expand
90,115 mg.	lactor subydross DT	_	87.70 mg.	lactore anhydrous DT
9,100 =-6	pregelationed starch N.F.	15	11.74 mg.	pregotationed storch N.F.
0.500 tog.	magnesius steurate N.F.	•	<u>0.50</u> mg.	engenius suurste N.F.
	total weight		100.013 mg.	noted weight
100.000 =1				ord Stage 7 Tablets
			0.035 ===	17 a-chi-ylestradiol
			0.010 mg.	d-acramite)
	EXAMPLE 5	20	29.500 mg.	inctose anhydrous [37]
	- a-bles for much stages		9.93 mg.	pregentinized starch N.F.
omposition of a	s tablet for each stage:		0.50 mg.	angresson messase N.F.
			100.015 mg.	total weight
	Ist Suge 7 Tablets			
0.035 ===	17a-minnyles-radiol	25		EXAMPLE 8
0.250 mg	sorcibiedroce			EAAMILE 0
88.9 mg.	incine anhydrous DT		Composition of a	tablet for each stage:
10.32 mg.	pregniations of surch N.F.			
0.5 mg.	magnesium scenate N.F.			
100.006 mg	total weight	30	<u> </u>	In Stage 7 Tablets
	2nd Stage 7 Tables	. –	0.035 mg.	17e-enisyles maiol
0.035 mg.	17e-ethinylestradiol		0.010 mg.	الشكامان وروو
0.375 mg.	marechindrone		90.200 mg.	lactore enhydrous DT
15.70 mg	lectors subjection DT		9.18 mg.	pregelationed starch N.F.
10.79 ME	pregelationed starch N.F.		0.50 mg.	magnesium measure N.F.
0.5 mg.	magnessen mearate N.F.	35)00.005 mg.	ental weight
160,000 mg	soral weight	•		2nd Stage 7 Tablets
tonion nation	3rd Stage 7 Tablets		0.035 ma.	17a-chisylestradiol
A 514	17g-ethicylestradiol		0.100 mg.	en:presinete
0.035 mg.	acrechindrone		10.150 mg.	lector unhydrous DT
0.5QD mg.	to a false on our		PA 130 MIG	N.F.

9.23 mg. 28.5 mg. lactors anhydrous DT 40 0.50 mg. pregetalisated march N.F. 10.47 mg. magnetium stewate N.F. 100.015 mg. 0.5 mg. Not Singe 7 Tablets total weight 100.005 mg. 0.035 mg. 17g-chinylent/1 0.125 👊 <u>sorgenti</u> 90.115 🛶 **EXAMPLE 6** 45 inized starch N.F. 9.230 mg. picarate N.F. 0.500 mg. Composition of a tablet for each stage: لطونوب لصمد 100.005

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•	1st Stage 7 Tableta
0.035 mg.	17g-eshin ylastradiol
0.05 =4	D-eorganid
90.0 mg.	lectors enhydrous DT
9.43 mg.	pregelemented starch N.F.
0.5 mg	magnesium steamte N.F.
100,015 =4	sosal weight
	2nd Stage 7 Tablets
0.035 mg.	17a-cthinylestradiol
0.073 106	D-sorpettel
\$7.70 mg.	tectore anhydrous DT
11.69 mg.	preschinated starch N.F.
0.5 mg.	ragamium sterrate N.F.
100,000 eng.	total weight
100000	3rd Stage 7 Tablets
0.035 ms.	17a-cikinylestradiol
0.100 mg.	D-eorgenited
99.5 mg	
9.84 mg.	pregentialized march N.P.
03 94	magnetium prostate N.F.
100,015	enal weight
1011013 146	200 -1-2-1

Clinical Tests **EXAMPLE 9**

A preparation according to Example 1 was administered in three separate studies to a total of 656 women of 55 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 60 in preventing pregnancy. In each study the bleeding pattern consistently showed a decrease in the incidence of mideycle breakthrough bleeding and/or spotting.

Having orscribed the invention in specific detail and exemplified the manner in which it may be carried into 65 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 4,544,554

be understood thathe foregoing is merely exemplary and the present mention is not to be limited to the specific form or arangements of parts herein described and shown.

I claim;

- 1. A method of intraception which comprises administering for 23 successive days to a female of childbearing age a wenbination of an estrogen and a progestogen in a loobist contraceptively effective daily dosage corresponding in extrogenic activity to 0.02-0.05 mg of Ta-ethinylestradiol and in progestogenic activity to 0.8840.75 mg of norethindrone for 5-8 days; for the next 71% days an estrogen daily dosage equal to 0.02-0.65mg of 17a-ethinylestradiol and in 15 progestogenic acavity to 0.250-1.0 mg of norethindrone, and for themat 3-7 days an estrogen daily dosage equal to 0.02-0.8 mg of 17a-ethinylestradiol and in progestogenic acarity 0.35-2.0 mg of norethindrone; followed by 6-8 days without estrogen and progestogen 20 administration, provided that the estrogen daily dosage is the same for eachperiod.
- The methodol'claim 1 wherein the estrogen and progestogen are administered orally and the period specified in each base is seven days.

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

- 4. The methody claim I wherein the progestogen is selected from Daorgestrel, norethindrone, progester- 30 one and D-17β-extraxy-13β-ethyl-17α-ethinyl-gon-4-en-3-one oxime.
- The method of claim 3 wherein the extrogen is selected from #h-ethinylestradiol, extrone, extradiol and extriol.

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

7. The method of claim 1 wherein the estrogen is 5 17α-ethinylestradiol and the progestogen is D-17βacetoxy-13\beta-ethyl-17a-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 17a-ethinylestradiol and norethindrone in a contraceptively effective daily dosage corresponding to 0.035 mg of 17α ethinylestradiol and 0.50 mg of porethindrone for 7 days; for the next 7 days a daily dosage equal to 0.035 mg of 17a-ethinylestradiol and 0.75 mg of porethindrone; and for the next 7 days a daily dreage equal to 0.035 mg of 17a-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 17a-ethinylestradiol and norgestimate in a contraceptively effective daily dosage corresponding to 0.035 mg of 17a-ethinylestradiol and 0.180 mg of norgestimate for 7 days; for the next 7 days a daily dosage equal to 0.035 mg of 17a-ethinylestradiol and 0.215 mg of norgestimate; and for the next 7 days a daily dosage equal to 0.035 mg of 17a-ethinylestradiol and 0.250 mg of norgestimate; followed by 7 days without estrogen and progestogen administration.

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United States Patent [19]

Pasquale

[11] Patent Number:

4,616,006

[45] Date of Patent:

Oct. 7, 1986

[54]	TRIPHASI	C 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
	Reis	ted U.S. Application Data
[63]	No. 4,544,5	m of Ser. No. 607,038, May 4, 1984. Pat. 34, which is a continuation-in-part of Ser. 3, Sep. 26, 1983, abandoned.
[51]	int. Cl.4	A01N-45/00; A61K 31/56
[52]	U.S. Cl	514/170
[58]	Field of Se	arch 514/170
[56]		References Cited
	U.S.	PATENT DOCUMENTS

4.530.839 7/1985 Pasquale 514/171

Primary Examiner—Elbert L. Roberts Attorney. Agent, or Firm—Benjamin F. Lambert

7] 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 17aethinylestradiol 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 dorage 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 extrogen 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 5 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 10 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 con- 15 trolling 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 20 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, 30 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 35 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 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 45 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 50 progestogen dozage 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 60 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 contra- 65 ception 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 men-25 struction occurs again. The cycle usually lasts 28 days but it may be sliightly longer or shorter. In acrual 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 combinations of various types are described in U.S. Pat. 40 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 extrogen 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 17a-ethinylestradiol. The preferred dosage is one equal 55 to a daily dosage of about 0.035 mg of 17a-ethinylestradiol.

In addition to 17a-ethinylestradiol, esters and ethers of 17a-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 pre-(erred estragen is 17a-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 35 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 50 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:

		60
	Ist Stage 7 Tablets	_
0.035 mg. 0.50 mg. 88.9 mg. 10.0 mg. 0.5 mg. 99.915 mg.	17e-ethinylestradiot morethindrone tactoes anhydrous DT pregelatisised starch N.F. magnesium stearate N.F. total weight	65

2nd Stage 7 Tablets		
0.035 mg. 0.75 mg. 82.70 mg. 10.02 mg. 0.5 mg.	170-ethinylestradiol norethindrone lactose anhydrous DT pregelatinized starch N.F. magnesium stearate N.F. total weight	

3rd	Stage 7 Tablets
0.035 mg. 1.0 mg. 48.5 mg. 10.0 mg.	17e-ethinylestradiol agrethindrone lactore ashydrous DT pregelatimized starch N.F.
0.5 <u>mg.</u>	magnesium stearste N.F.
100.035 mg.	total weight

EXAMPLE 2 Composition of a tablet for each stage:

		lui Stage 7 Tablets
0.035	mr.	17a-ethinylestradiol
	_	D-176-acctosy-136-ethyl-176-ethinyl-gon-4-en-
	-)-one oxime
#7.9	mg.	lactors anhydrous DT
*.1	mg.	pregelatinized starch N.F.
0.3	mr.	magnetium steirate N.F.
100 035	mg.	rotal weight
	0.50 #7. 7 1.1 0.3	11 mg. 11 mg. 03 mg.

5		
		2nd Stage 7 Tablets
	0.035 mg. 0.75 mg.	17a-ethinylestradiol D-17B-ectory-13B-ethyl-17a-ethinyl-gon-4-ss- 3-one oxime
0	\$1,70 mg. 1,02 mg. 0,5 mg.	become anhydrous DT programmen starch N.F. magnesium starrate N.F.
	100.005 mg.	total weight

3rd Stage 7 Tablets		
0.035 mg. 1.0 mg.	17a-ethinylestradioi D-17 <i>B-ace</i> toxy-13 <i>B-e</i> thyi-17a-ethinyi- gos 4-en -	
87.5 mg.	3-cme oxime lacuse anhydrous DT pregelatinized storch N.F.	
0.5 mg.	magnesium stearste N.F.	

EXAMPLE 3

Composition of a tablet for each stage:

۰ —	jet Stage 7 Tablets		
65	0.035 mg. 0.50 mg. 700 mg. 9.0 mg. 0.5 mg. 100.035 mg.	17a-ethinylestradiol D-norgestral hetone unhydrous DT pregeletinized starch N.F. magnesium steerate N.F. total weight	

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		ontinued
	2nd Si	age 7 Tablets
	10.39 mg.	pregetatinized starch N.F. magnesium ptenrate N.F.
	0.5 mg.	total weight
	TQUILLE WIGH	
	3rd S	cage 7 Tableta
	0.035 mg.) 7 ₀ -ethiny lestradiol worethind runt
	0.500 mg. 88.5 mg.	lactore anhydrous DT
	10.47 mg.	pregelatinized starch N.F. magnesium stearate N.F.
i	0.5 mg. 100.005 mg.	rores meiligs
		AMPLE 6
, c	omposition of a tab	let for each stage:
	lg:	Stage 7 Tablets
	0.035 mg.	17a-ethinylestradiol D-norgestral
5	0.05 mg. 70.0 mg.	factors anhydrous DT
	9.43 mg	pregelatinized starch N.F. magnesium stearate N.F.
	0.5 <u>\$18.</u> 100.015 mg.	total weight
	1.00	
)		
_	2md	Stage 7 Tablets
	0.035 mg.	(7a-ethinylestradio)
_	0.075 mg. \$7,70 mg.	D-norgestrel lactost anhydrout DT
5	11.69 mg-	pregelationed starck N.F.
	0.5 ma.	magnesium stearate N.F. total weight
	100.005 mg.	forth weight
۰		
_		d Stage 7 Tablets 17g-ethinylestradiol
	0.035 mg. 0.100 mg.	D-norgestrei
	27.5 mg.	lectors anhydrous DT pregeletinised starth N.F.
45	9.88 ang. 0.5 <u>ma.</u>	magnesium steerate N.F.
_	100.015 mg.	mini weight
	t	EXAMPLE 7
50		ablet for each stage:
_		st Stage 7 Tablets
55 —	0.0)5 mg.	17a-ethiaylestradiol
	0.025 mg.	D-norgenrei
	90.00 mg. 9.45 mg.	lectore anhydrous DT pregeletinized march N.F.
	9.45 mg. 0.50 mg.	megnesium steatute N.F.
60 -	100.000 mg.	sotal weight
ov —		
-		2nd Stage 7 Tablets
65 -	0.035 mg.	(74-mhisyleszadiól
~~	0.036 mg. 87,70 mg.	D-norgestrel Inctore anhydrous DT
		accordance and starth N.F.

0.035	mr.	17a-erbinylestradiol
0.73	mg.	D-norgestre)
87.70	mg.	jectore anhydrous DT
11.02	mg.	pregelatinized starch N.F.
0.5	mg.	magnesium stearate N.F.
10.005		total weight
)n	d Stage 7 Toblets
0.035		
0.035	mg.	d Stage 7 Tablets 17a-ethinylestradiol D-norgested
1.0	mg. mg.	17a-ethinylestradiol
	mg.	17a-ethinylestradiol D-norgentel

EXAMPLE 4

total weight

Composition of a tablet for each stage:

100.035 #g.

	k Stage 7 Tablets
0.035 mg.	170-ethinylestradiol
0.180 mg.	oorgasimukt
90.200 mg.	lactors enhydrous DT
9.085 mg.	pregelatioused starch N.F.
0.500 mg	magnesium stearate N.F.
100.000 eng.	total weight

	·
	2nd Stage 7 Tables
0.035 m	17e-ethinylestradiol
0.215 m	norgatimete
#0.150 m	lectore enkydrous DT
7.100 m	ereneintwice starch N.F.
0.500 m	
100,000 =0	

 	3rd Stage ? Tableta
0.035 mg. 0.250 mg. 90.115 mg. 9.100 mg. 0.500 mg.	170-ethinylestradiol norgestanate lectore anhydrous DT pregelationated starch N.F. anagaments starch N.F.
100.000 mg.	total weight

EXAMPLE 5

Composition of a tablet for each stage:

	1st Stage 7 Tablets	
0.035 mg. 0.250 mg. 81.9 mg. 10.32 mg. 0.5 mg. 100.006 mg.	17g-ethinylestradiol norethindrone lactore anhydrous DT pregelatinized starch N.F magnesium stearate N.F. total weight	···

 	· · · · · · · · · · · · · · · · · · ·	65
	2nd Stage 7 Tablets	``
0.035 mg. 0.375 mg. 8.70 mg.	(7a-mhinylestradio) sorethindrone lactose anhydrous DT	

	1st Stage 7 Tablets
0.035 mg	17a-ethioylestradiol
0.025 mg.	D-norgenrei
90.00 mg.	lectore anhydrous DT
9.45 mg-	pregeletinized march N.F.
0.50 mg.	magnesium stearate N.F.
100.000 mg.	sotal weight

	2nd Stage 7 Tablets
0.035 mg. 0.038 mg. 87.70 mg. 11.74 mg. 0.50 mg.	17s-ethiopiestradiol D-norgestral lectors unhydrous DT prepalatinized starch N.F. magnesium steares N.F.

-continued 2nd Stage 7 Tabless		
		100.013 mg.
100.013 mg.	toul weight	

)m	d Stage 7 Tablets	
0.035 mg.	17a-ethinylestradiol	
0.050 mg.	D-worgestrel	10
29.500 mg.	lactore anhydrous DT	
9.93 mg.	pregelatinized starch N.F.	
0.50 mg	magnesium stearage N.F.	
100.015 mg.	total weight	

EXAMPLE 8

Composition of a tablet for each stage:

1st Stage 7 Tableta		<u> </u>
0.035 mg.	17a-ethinylestradiol	
0,090 mg.	norgestimale	
90,200 mg.	lactors anhydrous DT	
9.1\$ tng.	prepelatinized starch N.F.	
<u>0.50 mg.</u>	magnesium stearare N.F.	25
100.005 mg.	total weigh t	

	2nd Stage 7 Tablets
0.035 mg.	17a -ethiny lestraden
0.100 mg.	norgestimate
90.150 mg.	lectors anhydrous DT
9.23 mg.	pregelatinized starch N.F.
<u>0.50 mg.</u>	magnesium steatate N.F.
100,015 mg.	total weight

3rc	3rd Stage 7 Tablets		
0.035 mg	17a-ethinylestradiol		
0.125 mg.	norgenimale		
90.115 mg.	lactore anhydrous DT		
9.130 mg.	pregulationzed 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 53 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 mideycle 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 65 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:

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 17a-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 17a-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 extrogen at a contraceptively effective dotage corresponding to 0.02-0.05 mg of 17a-ethinylestradioi 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.
- The unit according to claim 1 wherein the dozage 30 units are in the form of tablets.
 - The unit according to claim 1 wherein the estrogen is selected from 17α-ethinylestradiol, estrone, estradiol and estriol.
- The unit according to claim 2 wherein the estrogen
 is 17a-ethinylestradiol.
 - 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.
 - The unit according to claim 5 wherein the progestogen is norethindrone.
 - The unit according to claim 5 wherein the progestogen is D-17β-acetoxy-13β-ethyl-17α-ethinyl-gon-4en-3-one oxime.
- 45 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 17a-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.
- 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 17a-ethinylestradiol and in progestogenic activity to 0.065-0.75 mg of norethindrone as the first phase; followed by 7-11 dosage