CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 20-713

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Clinical Pharmacology Biopharmaceutics Review(s)	X			
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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20-713

Trade Name: MIRCETTE TABLETS

Generic Name:(desogestrel/ethinyl estradiol and ethinyl estradiol)

Sponsor: Organon, Inc.

Approval Date: April 22, 1998

Indication: Provides for the prevention of pregnancy

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20-713

APPROVAL LETTER

DF

NDA 20-713

Organon, Inc.
Attention: Mr. Albert Mayo
Director, Regulatory Affairs
375 Mount Pleasant Avenue
West Orange, NJ 07052

APR 22 1998

Dear Mr. Mayo:

Please refer to your new drug application dated April 30, 1997, received April 30, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mircette (desogestrel/ethinyl estradiol and ethinyl estradiol) Tablets.

We acknowledge receipt of your submissions dated August 29, September 30, October 8, November 26 and 28 and December 31, 1997; January 8, 12, 13, and 15, February 3, March 5, 12, and 26, and April 14, and 16 (3), 1998. The User Fee goal date for this application is April 30, 1998.

This new drug application provides for the prevention of pregnancy.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated April 16, 1998. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on April 16, 1998. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-713. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in your submission dated April 14, 1998. These commitments, along with any completion dates agreed upon, are listed below.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocol, data, and final reports to this NDA as correspondences. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to this application, a status summary of each commitment. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Christina Kish, Project Manager, at (301) 827-4260.

Sincerely,

/S/ 4/22/94

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-713
HFD-580/Div. files
HFD-580/CSO/C.Kish
HFD-580/MMann/LRarick/MRhee/DLin/AJordan/ADorantes/VJarugula/
LKammerman
HFD-713/MNg
HFD-002/ORM (with labeling)
HFD-102/Office Director (with labeling)
HFD-101/L.Carter
HFD-820/ONDC Division Director
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling)
HFI-20/Press Office (with labeling)
HFD-580/CKish/3.27.98/n20713ap.

APPROVAL (AP) [with Phase 4 Commitments]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-713

MEDICAL REVIEW(S)

NDA: 20-713

FEB 18 1998

Medical Officer's Review
(Original NDA)

Date submitted: 4/30/97
Date received: 4/30/97
Date assigned: 5/6/97
MOR completed 1/16/98

Sponsor: Organon Inc.
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Drug:

Generic	Desogestrel/ethinyl estradiol and ethinyl estradiol
Trade:	CTR 25
Chemical:	13-ethyl-11-methylene-18,19-dinor-17 alpha-pregn-4-en-20-yn-17-ol

Route: Oral

Dosage form: Oral tablet

Strength:

Days 1-21:	150 mcg desogestrel/20 mcg ethinyl estradiol
Days 22-23:	placebo
Days 24-28:	10 mcg ethinyl estradiol

Proposed indication: Contraception

Related INDs: IND
IND
IND

All three INDs were for desogestrel and ethinyl estradiol tablets and were sponsored by Organon

Related NDAs: NDA 20-071 CTR 04 - Desogen - marketed product

TABLE OF CONTENTS

SECTION AND TOPIC PAGE

1.0 Resume

This submission is for a new oral contraceptive (CTR 25) similar to Desogen, already on the U.S. market. CTR 25 contains 150 mcg desogestrel on days 1-21 like Desogen. However, the dose of ethinyl estradiol (EE) is only 20 mcg on days 1-21, lower than the 30 mcg in Desogen. The dose has been lowered in the hope of improving the safety profile compared with Desogen in terms of thrombosis and cardiovascular disease. Lowering the dose could, however, lead to poorer efficacy and cycle control, so a daily dose of 10 mcg EE alone has been added to days 24-28, which are placebo days in the Desogen formulation. This addition of five days of (admittedly a small dose of) unopposed estrogen raises at least the theoretical possibility of an increased risk of endometrial hyperplasia.

The submission includes one pivotal study of contraceptive efficacy and two smaller studies to assess follicular development and bleeding patterns.

Within the pivotal study, there are seven substudies which evaluated lipids, endocrine effects, endometrial morphology, carbohydrate metabolism, steady state PK, hemostasis/ fibrinolysis, and ophthalmic conditions. The study was an open-label, noncomparative study conducted in 33 centers in the United States. Half the subjects were to be Starters (no OC use in the two months immediately preceding study entry) and half Switchers from other combined OCS. The women had to meet the usual entry criteria for enrollment.

Women were followed every three months for 18 cycles. Endpoints included contraceptive efficacy, bleeding patterns, and safety.

A total of 1226 women enrolled and took study drug. Of these, 663 (53%) took study drug for at least 13 cycles and 327 completed 18 cycles. There were a total of 14,050 cycles of exposure, thus the targets of 200 women completing 13 cycles and a total of 10,000 cycles were achieved.

Patterns of discontinuation and compliance were as expected for an OC study.

The Pearl rate using all 14050 cycles of exposure was 1.11 pregnancies per 100 woman-years. The life table rate for the first 13 cycles was also 1.11.

The pattern of AEs was consistent with that seen with other OCs and does not raise safety concerns regarding this product. There were no deaths, myocardial infarctions, pulmonary emboli, strokes, or deep vein thromboses.

A comparison with marketed OCs suggests that CTR 25 causes about the same incidence of breakthrough bleeding/spotting as other 20 mcg EE pills, and more than Desogen which contains 30 mcg EE.

The objective of the endometrial histology substudy was to assess the effect of CTR 25 on endometrial histology in 40 subjects (Starters) over 13 months at three centers. Biopsies were to be done at baseline, in cycle 13 (days 18-21) and cycle 14 (days 1-4). However, only 14 of the intended 40 subjects were biopsied at the correct time points in both cycle 13 and cycle 14. Additional subjects contributed data which are considered relevant to the study objective and resulted in a total of 20 biopsies from cycle 13 (4 done at the incorrect time) and 16 biopsies from cycle 14 (one of which was really taken in cycle 15). This falls far short of the intended 40 biopsies at each time point. There were no cases of hyperplasia seen, but the study was completely inadequate to evaluate this risk. It is recommended that a study to better assess the risk of

hyperplasia in women who complete 12 cycles plus 4 days and undergo endometrial biopsy at baseline and during days 1-4 of cycle 13 be made a Phase IV requirement for approval.

The objective of the hemostasis and fibrinolysis substudy was to evaluate the effect of CTR 25 on Prothrombin time, APPT, fibrinogen, D-dimer (fibrin split products), plasminogen activator inhibitor 1 and total, antithrombin III, Factor VII, plasminogen, and fibrin degradation products in 100 patients (starters) baseline, cycle 3, and cycle 6.

Values for D-dimer were above normal at baseline, increased at cycle 3, and fell but remained outside the normal range at cycle 6. Mean values for Factor VII were outside the normal range at baseline and cycle 3. All other parameters were within the normal range at baseline and during test cycles.

The results in this subset probably are not cause for concern, especially since there were no AEs related to thrombus formation. However, an official consult with the Division of Gastrointestinal and Coagulation Drug Products to further evaluate the significance of the D-dimer and Factor VII results is recommended.

The lipid profile, endocrine, ophthalmology, and carbohydrate substudies do not suggest a deleterious effect from this OC.

The supporting studies included one that evaluated follicular development and one that evaluated bleeding patterns. The objective of the first study was to determine the effect of adding 5 days of EE 10 mcg on days 24-28 to the formulation consisting of 150 mcg DSG and 20 mcg EE on days 1-21. Endpoints included ultrasound, estradiol, progesterone, FSH, LH, EE, and vaginal bleeding patterns. It was done at one center in the UK. The study showed a nonsignificant difference in follicular development that favored CTR 25.

The second study was designed to look at bleeding patterns and enrolled 200 women in each of two groups at ten European centers. Both groups received 21 days of desogestrel 150 mcg. The CTR 25 group received two days of placebo followed by 5 days of EE 10 mcg on cycle days 24-28. The placebo group received seven placebo tablets from days 22-28. Women were followed for six cycles. The endpoint was bleeding patterns as recorded on daily diaries. This study failed to show that the addition of the 10 mcg EE improves overall bleeding patterns.

While the product appears effective, the studies failed to show that the addition of EE on days 24-28 improves follicular suppression or cycle control compared with not administering EE during this time. This formulation therefore offers no advantages over existing ones. The risk of endometrial hyperplasia that theoretically ensues from the addition of five days of unopposed estrogen has not been adequately evaluated. Approval is recommended with the requirement for a study to better assess the risk of endometrial hyperplasia in women who complete 12 cycles plus 4 days and undergo endometrial biopsy at baseline and during days 1-4 of cycle 13.

2.0 Background

Desogestrel is one of three new progestins used in OCs[1]. It has a high progestational activity, no estrogenic activity and only weak androgenic activity, making it less likely than some other progestins to cause unfavorable effects on lipids. There are currently two OC formulations containing desogestrel on the world market, both of which are monophasic and contain 150 mcg desogestrel (see table below). Desogen, sold in the US, and Marvelon, sold in Europe, both contain 30 mcg ethinyl estradiol. Mercilon, sold in Europe, contains 20 mcg ethinyl estradiol. There are currently only two OCs on the market in the U.S. that contain 20 mcg EE (Alesse and Loestrin1/20).

Content of selected OCs

Brand name	days 1-21	days 22-23	days 24-28
Desogen/Marvelon	DSG 150/EE 30	placebo	
Mercilon	DSG 150/EE 20	placebo	
CTR 25	" "	placebo	EE 10
Alesse	LNG 100/EE 20	placebo	
Loestrin 1/20	NET 1000/EE 20	placebo	

CTR-25 contains 150 mcg desogestrel and 20 mcg ethinyl estradiol for 21 days, like Mercilon. However the 21 days are followed by 2 placebo tablets and then five tablets containing 10 mcg ethinyl estradiol alone. "The primary aim of this regimen is to further suppress ovarian function to the point where contraceptive efficacy is not compromised if a pill is missed at the beginning of the next cycle. The regimen also aims to maintain a pattern of regular menstrual bleeding approximately every 28 days utilizing a reduction in the level of EE as compared with 30 mcg EE-containing oral contraceptives, such as Desogen." (Page 0103, vol 1.2) The five days of EE suppress FSH and stimulate the proliferation of epithelial cells and induce progestin receptor sites, which may improve cycle control .

The lower dosage of EE in Mercilon compared with Marvelon may be responsible for poorer cycle control although efficacy does not appear to differ. There have been several comparative trials of Marvelon and Mercilon. In a study of 1000 women[ref 1] followed for one year, Pearl rates were 0.6 for Marvelon and 0.4 for Mercilon. However, both pregnancies in the Mercilon group and two of three in the Marvelon group were attributed to user failure. Breakthrough bleeding was more common in the Mercilon group. Among women not using oral contraceptives immediately before enrollment (Starters), the difference reached significance by the third cycle (Mercilon 28.8% vs Marvelon 18.8%). For women who switched from another oral contraceptive at the time of enrollment (Switchers), the difference was significant for each of the first three cycles, with 21.9% of Mercilon users and 16.3% of Marvelon users reporting BTB in the third cycle. Overall, a

[1] The other two are norgestimate and gestodene; the three are sometimes referred to as "third generation" progestins although this derives from the fact that they appeared on the market at roughly the same time rather than from any pharmacologic resemblance.

difference was seen in all cycles and reached statistical significance in two thirds of them. There were no differences in blood pressure, weight change or hemoglobin between the groups. Dizziness and mood changes were more common in the Mercilon group.

Late in 1995, reports linking OCs containing gestodene and desogestrel with venous and arterial thrombotic events were published. The World Health Organization convened a meeting of scientific experts in November 1997 to consider the safety of the new progestins. They concluded that, "Combined OC preparations containing desogestrel and gestodene probably carry a small risk of venous thromboembolism beyond that attributable to combined OCs containing levonorgestrel. There are insufficient data to draw conclusions with regard to combined OCs containing norgestimate." In addition, the group concluded, "The suggestion that gestodene- or desogestrel-containing low dose combined OCs may carry a lower risk of myocardial infarction compared with low dose formulations containing levonorgestrel remains to be substantiated."

Some studies[refs 2,3,4,5] suggest that the reduced EE dose in Mercilon compared with Marvelon results in a change in coagulation factors consistent with a reduced risk of thrombus formation and small differences in lipids consistent with a reduced risk of cardiovascular disease among Mercilon users.

It appears that the sponsor of CTR 25 is trying to achieve a formulation with the possible safety advantages of Mercilon without its cycle control problems and (theoretically) reduced efficacy. The monthly dose of EE in Mercilon is 420 mcg compared with 630 mcg with Marvelon. The monthly dose of EE in CTR 25 is 470 mcg, only 12% more than that of Mercilon, but placement of this additional amount in effect preceding each pack could have the desired effect of improving efficacy especially if a pill is missed early in the cycle and improving cycle control.

2.1 Regulatory history

CTR-25

The agency received IND containing the protocol for this study on 8/27/93. It called for a 2 year open label study of 1200 women at 30-40 sites in the U.S. for up to 18 cycles, with 200 women to complete 13 cycles. The endpoints would be efficacy, bleeding, and safety. There would be seven substudies to evaluate lipids, endocrine effects, endometrial morphology, carbohydrate metabolism, steady state PK, hemostasis/ fibrinolysis, and ophthalmic conditions.

The medical reviewer raised questions concerning instructions for missed pills, inclusion criteria having to do with smoking, and use of antibiotics during the study. All were resolved to the agency's satisfaction. No issues were raised regarding the endometrial biopsy subset.

CTR-05 (TriDesogen)

This formulation contained 50/100/150 mcg desogestrel and 35/30/30 mcg ethinyl estradiol in a 7/7/7 day regimen.

CTR-04 (Desogen in U.S., Marvelon approved in 70 countries)

NDA 20-071 was submitted on April 10, 1992 and approved on December 10, 1992. The Pearl index was 1.14 which was felt to be somewhat high but acceptable. Headaches and dysmenorrhea were more frequent than in other OC studies, but this was felt to be the result of ascertainment bias.

2.2 Preclinical studies

The non-clinical section of this NDA is included by cross-reference to the same in the Desogen and Tri-Desogen NDAs and INDs.

2.3 Human pharmacology studies

The following studies were conducted:

#086-002 "A Single Dose Study of the Bioavailability of CTR-25 (150 mcg DOG/20 mcg EE tablet) Relative to a Combination Solution"- vol 28-32

#86-003 " Single Dose Study of the Bioavailability of CTR 25 (10 mcg EE tablet) Relative to an EE Solution - vol 33-36

Please see separate biopharm review.

2.4 International marketing experience

Marvelon was first approved in 1981 in Germany. It has since been approved in over 70 countries. Mercilon was approved in Great Britain in 1986 and has since been approved in approximately 50 countries.

Late in 1995, reports linking OCS containing gestodene and desogestrel with venous and arterial thrombotic events were published. As a result, prescription of such OCS to first- time users was prohibited by court order in Germany in December 1995. This ban was lifted on December 19, 1997 in view of new research.

3. Summary of NDA clinical section

3.1 Summary of uncontrolled trials

- *Protocol 086-001*
  An open-label multi center non-comparative safety and efficacy study of the desogestrel containing oral contracep
  CTR 25 - vol 37-59

  The objective of this pivotal study was to evaluate the contraceptive efficacy, vaginal bleeding patterns, and safety in 1200 women completing a minimum of 10,000 cycles and 200 women completing 13 cycles. Seven subsets of patients were studied for effects on hemostasis and fibrinolysis, ophthalmologic conditions, lipid profiles, endocrine profiles, endometrial morphology, carbohydrate metabolism, and steady state pharmacokinetics parameters. It was an open-label, noncomparative study conducted in 33 centers in the United States. Half the subjects were to be Starters (no OC use in the two months immediately preceding study entry) and half Switchers from

other combined OCS. Women had to meet the usual inclusion/exclusion criteria to be enrolled.

Women were followed every three months for 18 cycles. Endpoints included contraceptive efficacy, bleeding patterns, and safety.

A total of 1226 women enrolled and took study drug. 663 (53% of those enrolled) took study drug for at least 13 cycles and 327 completed 18 cycles. There were a total of 14050 cycles of exposure, thus the target of 200 women completing 13 cycles and a total of 10,000 cycles were achieved.

The study population was 90% Caucasian and had an average age of 28.3 and BMI of 23.5 kg/m^2. Sixty-five per cent were nulliparous, 86% smoked three or fewer cigarettes per day, and the average mean coital frequency was about 9.2 acts per month. There were no important differences between Starters and Switchers except in previous contraceptive use. A larger proportion of Starters reported having used barrier methods in the past (95.6% vs 74.4%, respectively). However, 85.3% of Starters had used OCS at some point in the past.

Patterns of discontinuation and compliance were as expected for an OC study.

Pregnancy was suspected or confirmed in 77 volunteers. Of these, pregnancy was confirmed in 45; 11 during study drug administration, 9 prior to start of study drug, and 25 after discontinuation of study drug. A thorough review of all pregnancies did not reveal any which were misclassified as to the time of conception relative to taking if study drug. Three of the 11 women with in-study pregnancies reported having taken their pills incorrectly in the cycle in which they conceived.

The Pearl rate using all 14050 cycles of exposure is 1.11 pregnancies per 100 woman-years. The life table rate for the first 13 cycles happens to also be 1.11.

Of the 1226 subjects in the All-Subjects-Treated group, 902 (73.6%) reported at least one AE. Five hundred thirty-eight (43.9%) reported an AE related to study drug. Twenty-nine subjects (2.4%) reported a total of 31 serious AE (2.3% of Switchers and 2.4% of Starters). Two SAEs (one case of depression and one case of cholecystitis) were considered by the investigator to be possibly related to the study drug. There were no deaths, myocardial infarctions, pulmonary emboli, strokes, or deep vein thromboses.

The system-organ class with the greatest number of non-serious AEs related to study drug was the reproductive tract. Within this class, the most common study drug related AEs were intermenstrual bleeding (7.3% of subjects), breast pain (4.6% of subjects), and dysmenorrhea and menstrual disorder (4.2% of subjects each). Moniliasis was the most common reproductive tract AE not related to study drug, reported by 6.7% of subjects. Headache was the most frequently reported AE, *disregarding* relatedness to study drug, occurring in 17.9% of subjects.

One hundred forty nine subjects (12.2% of 1226 total) discontinued due to an AE. The pattern of AEs is consistent with that seen with other OCs and does not raise safety concerns regarding this product.

About 85% of subjects experienced the expected spotting or bleeding during the desogestrel- free period in cycle 3. This dropped to about 80% of subjects by cycle 6 and remained steady through

cycle 18. In 8 to 12% of subjects, bleeding began early, before the desogestrel-free period. This pattern held until Cycle 15 when the percent dropped to about 5%. In about 10% of subjects, bleeding continued into the first 2-3 days of the desogestrel-free period. This pattern persisted through cycle 18. Thirty-six subjects (2.9%) discontinued primarily due to menstrual problems.

A comparison with marketed OCs suggests that CTR 25 causes about the same incidence of breakthrough bleeding/spotting as other 20 mcg EE pills, and more than Desogen which contains 30 mcg EE.

The objective of the endometrial histology substudy was to assess the effect of CTR 25 on endometrial histology in 40 subjects (Starters) over 13 months at three centers. Biopsies were to be done at baseline, in cycle 13 (days 18-21) and cycle 14 (days 1-4). However, only 14 of the intended 40 subjects were biopsied at the correct time points in both cycle 13 and cycle 14. Additional subjects contributed data which are considered relevant to the study objective and resulted in a total of 20 biopsies from cycle 13 (4 done at the incorrect time) and 16 biopsies from cycle 14 (one of which was really taken in cycle 15). This falls far short of the intended 40 biopsies at each time point. There were no cases of hyperplasia seen, but the study was completely inadequate to evaluate this risk. It is recommended that a study to better assess the risk of hyperplasia in women who complete 12 cycles plus 4 days and undergo endometrial biopsy at baseline and during days 1-4 of cycle 13 be made a Phase IV requirement for approval.

The objective of this substudy was to evaluate the effect of CTR 25 on Prothrombin time, APPT, fibrinogen, D-dimer (fibrin split products), plasminogen activator inhibiter 1 and total, antithrombin III, Factor VII, plasminogen, and fibrin degradation products in 100 patients (Starters) at 10 sites at baseline, cycle 3, and cycle 6 between day 15 and day 21.

Ninety-nine subjects enrolled. Ninety-eight took at least one dose of study medication. Baseline characteristics did not differ in any important way from the main study population. Values for D-dimer were above normal at baseline (mean of 611.7 ng/ml with an upper limit of normal of <400 ng/ml.) The mean increased to 884.2 ng/ml at cycle 3 and fell to 595.7 ng/ml at cycle 6. Mean values for Factor VII were 148.2% at baseline, 162.3% at cycle 3, and 135.1% at cycle 6 (normal range 65-135%).

All other parameters were within the normal range at baseline and during test cycles.

The results in this subset probably are not cause for concern, especially since there were no AEs related to thrombus formation. However, an official consult with the Division of Gastrointestinal and Coagulation Drug Products to further evaluate the significance of the D-dimer and Factor VII results is recommended.

The lipid profile, endocrine, ophthalmology, and carbohydrate substudies do not suggest a deleterious effect from this OC.

The submitted data provide adequate assurance that CTR is safe and effective for marketing. It does not appear to offer advantages over Desogen or other OCs containing 20 mcg EE. The risk of endometrial hyperplasia has not been adequately addressed by Substudy C and should be studied in a Phase IV study, but this risk is very small and is not a sufficient reason to withhold approval.

3.2 Summary of controlled trials

- *Protocol 31904*
  A randomized, group comparative, double blind, placebo-controlled study of the pharmacodynamic effect of 10 ethinyl estradiol in the tablet-free period of a low-dose oral contraceptive - vol 27

  The objective of this study was to determine the effect of adding 5 days of EE 10 mcg on days 24-28 to the formulation consisting of 150 mcg DSG and 20 mcg EE on days 1-21. Endpoints included ultrasound, estradiol, progesterone, FSH, LH, EE, and vaginal bleeding patterns. It was done at one center in the UK.

  The study showed a nonsignificant difference in follicular development that favored CTR 25, as manifested by ultrasound results. CTR 25 users experienced more bleeding/spotting episodes but they were shorter and consisted of more spotting days than among placebo users.

- *Protocol 39801*
  A randomized, multi center comparative double blind placebo controlled study of the effect on the vaginal bleedi pattern of 10 mcg ethinyl estradiol in the tablet-free period of a low dose oral contraceptive - vol 60-61

  This study enrolled 200 women in each of two groups at ten European centers. Both groups received 21 days of desogestrel 150 mcg. The CTR 25 group received two days of placebo followed by 5 days of EE 10 mcg on cycle days 24-28. The placebo group received seven placebo tablets from days 22-28. Women were followed for six cycles.

  The endpoint was bleeding patterns as recorded on daily diaries.

  Breakthrough bleeding and/or spotting occurred in 23.2% of women in the placebo group in the first cycle, compared with 20.5% in the CTR 25 group. In cycles 2 through 6, however, breakthrough bleeding and/or spotting occurred in a greater proportion of patients in the CTR 25 group, due mostly to differences in spotting. Overall, breakthrough bleeding and/or spotting occurred in 15.9% of CTR 25 cycles compared with 12.4% of placebo cycles. The absence of withdrawal bleeding was somewhat higher in the CTR 25 group also. The duration of bleeding was similar in both groups.

  This study failed to show that the addition of the 10 mcg EE improves overall bleeding patterns.

4. PROTOCOL 086-001: AN OPEN-LABEL MULTI CENTER NON-COMPARATIVE SAFETY AND EFFICACY STUDY OF THE DESOGESTREL CONTAINING ORAL CONTRACEPTIVE CTR 25 (VOL 37-59)

4.1 Objective

The study objective was to evaluate the contraceptive efficacy, vaginal bleeding patterns, and safety in 1200 women completing a minimum of 10,000 cycles and 200 women completing 13 cycles. Seven subsets of patients were studied for effects on hemostasis and fibrinolysis (99 subjects), ophthalmologic conditions (55 subjects), lipid profiles (97 subjects), endocrine profiles (64 subjects), endometrial morphology (40 subjects), carbohydrate metabolism (32 subjects), and steady state pharmacokinetics parameters (24 subjects).

4.2 Design

This was an open-label, noncomparative study conducted in 33 centers in the United States. Approximately half the subjects were to be Starters (no OC use in the two months immediately preceding study entry) and half Switchers from other combined OCS.

4.3 Study population, inc/exc criteria

To be eligible, a woman had to be 18-50 years old, have had regular menses for the three months prior to entry, not be pregnant or breast-feeding but sexually active and at risk for pregnancy, and be willing to continue study drug for 18 cycles. She must have had no contraindications to combined OC use, not used an injectable hormonal contraceptive for six months, not used a progestin-releasing IUD for three months, and not used contraceptive implants for two months. In addition, she could not be outside the 80-130% range of ideal body weight, have taken lipid-altering drugs or drugs that affect steroid PK within 30 days prior to enrollment, have ever taken etretinate, have a systolic blood pressure $\geq$ 150 mm Hg or a diastolic blood pressure $\geq$ 90 mm Hg, had abnormal findings on pelvic or breast exam that precluded participation, have ASCUS or more severe findings on Pap smear, have significant cardiovascular, hepatic, or renal disease, diabetes, or a thyroid disorder. She must not have reported consuming more than two alcoholic beverages per day on average, smoking $\geq$15 cigarettes a day if $\geq$35 years old, having a history of drug abuse, or taking an investigational drug within 90 days.

4.4 Procedures, randomization

At screening, volunteers had blood drawn for serum pregnancy testing and chemistry and hematology profiles. They also underwent urinalysis and a complete physical exam including pelvic exam and Pap smear and breast exam. Paps were done in a central lab.

If eligible, a woman was dispensed 3 packs of 28 pills, to be resupplied at the end of cycles 3, 6, 9, 12, and 15. Starters were told to follow a Sunday-start regimen and were given urine pregnancy tests to use at home before initial administration of study drug. Switchers were also told to follow a Sunday start regimen regardless of whether they were Sunday starters on their current pill.

Missed pills were to be handled as follows. If a volunteer was late starting a pack, she was instructed to use backup contraception until 7 consecutive active pills had been taken. If a volunteer missed one or two consecutive tablets she was to take them as soon as she remembered, with backup contraception to be used for 7 days if two pills had been missed. If three consecutive or four pills in any one cycle were missed, the volunteer was discontinued.

> **Reviewer's comment:**
> **These instructions differ from those in the proposed labeling, which follows current OC class labeling (in the process of being revised). In current class labeling, if a woman misses two pills, she is to take two pills the day she remembers and two the next day, rather than taking both missed pills when she remembers them as stated in the protocol. In addition, in the class labeling, if a woman misses two pills in the third week, she is to skip the placebo period and start the next pack right away. No such instruction appears in this study protocol.**

Volunteers were seen every three months for vital signs, weight, interim history, collection of diaries,

reporting of AEs and concomitant therapies, and dispensing of study drug. The physical exam and labwork were repeated at the end of cycles 6, 12, and 18. A Pap smear and serum pregnancy test were done at the end of participation. At discontinuation from the study, volunteers were given two home urine pregnancy test kits to be used 14 days after the last tablet was taken and if the next withdrawal bleed was late. All volunteers were seen or contacted by phone three months after they left the study to determine whether they were pregnant, what contraception they were using, and whether there were any untoward events.

4.5 Endpoints

Contraceptive efficacy
Pregnancy tests were prompted by the failure of withdrawal bleeds ("when indicated"); tests were not done at every visit. The date of conception was determined by using the following information is descending order of priority: ultrasound, serum hCG in the first trimester, exam of the patient or products of conception or newborn, diary, and investigator estimate in the absence of other information. In-treatment pregnancies were those in which conception occurred after the first tablet was taken and prior to discontinuation of study drug.

Bleeding patterns:
Bleeding and spotting were recorded on diary cards. Bleeding was defined as any bloody discharge requiring more than one sanitary napkin or tampon per day. Spotting was any bloody discharge that did not require more than one napkin or tampon per day. Additional definitions may be found in Attachment A.

Safety
Adverse experiences (AEs), changes in physical exam and lab results, and pregnancy outcomes were reviewed to evaluate safety. Relatedness was considered definite if it "follows a reasonable temporal sequence from administration of study drug and confirmed by improvement on stopping the drug and reappearance of the reaction on repeated exposure". Relatedness was considered "probable" if "a relationship has not been clearly demonstrated but is likely" (p. 66, vol. 39).

> **Reviewers' comment: It is not likely that reexposure would occur in the context of this study. Therefore, the designation of "definitely related" is not likely to have been made in most cases. Thus, those events which are "probably related" may be more meaningful.**

4.6 Patient disposition

1250 subjects enrolled
1226 took study drug
- 585 (48%) were Starters contributing 42% of the total number of cycles
- 641 (52%) were Switchers who contributed 58% of the total number of cycles.

663 (53% of those enrolled) took study drug for at least 13 cycles
327 completed 18 cycles
- 108 (33%) were Starters
- 219 (67%) were Switchers

There were a total of 14050 cycles of exposure (a mean of 10.2 for Starters and 12.6 for Switchers).

> Reviewer's comment: Only 53% of those enrolled completed 13 months of study participation. This is a high attrition rate, but acceptable since the study achieved its goal of 200 women completing 13 cycles and 10,000 cycles of use.

4.7 Discontinuations

Table 7, p. 119, vol. 39 is reproduced below.

REASONS FOR DISCONTINUATION (before 18 cycles)
All-Subjects Treated Group

Reason for Discontinuation	Starters		Switchers		Total	
	N	%	N	%	N	%
Drug-related AE	70	12.0	56	8.7	126	10.3
Non-drug related reason	8	1.4	3	0.5	11	0.9
Reason unknown[2]	70	12.0	48	7.5	118	9.6
Pregnancy or suspicion thereof[3]	6	1.0	8	1.2	14	1.1
Personal reason	108	18.5	100	15.6	208	17.0
Study closeout	109	18.6	117	18.3	226	18.4
Non-compliance	75	12.8	51	8.0	126	10.3
Protocol violation	31	5.3	39	6.1	70	5.7
Total discontinued	477	81.5	422	65.8	899	73.3
Total entered	585	100.0	641	100.0	1226	100.0

Information for this table was derived from Data Listings 1 and 10.

Reviewer's comment:
The most common reason for failure to complete the study was study closeout. The next most common reason was personal. AEs accounted for 10.3% of discontinuations, which is not unusually high. Review of specific AEs (see below) does not raise safety issues. The "reason unknown" or lost to follow-up rate of 9.6% is acceptable, as is the non-compliance rate of 10.3%.

The table above summarizes reasons for discontinuation before 18 cycles. However, a similar table for discontinuations before 13 cycles (without distinguishing between Starters and Switchers) can be constructed from data in Table 8 on page 121 of Volume 39:

[2] "Reason unknown' was specified in the CRF as "Reason unknown (e.g. Lost to Follow-Up"

[3] Pregnancies include 11 in-treatment pregnancies and three pre-treatment pregnancies. The three pre-treatment pregnancies include one subject who took study drug while pregnant(and two subjects who did not take study drug

REASONS FOR DISCONTINUATION (before 13 cycles)
All-Subjects Treated Group

Reason for Discontinuation	Total	
	N	%
Drug-related AE	107	9.4
Non-drug related reason	9	0.8
Reason unknown	73	6.4
Pregnancy or suspicion thereof	9	0.8
Personal reason	158	13.8
Study closeout	0	0
Non-compliance	101	8.8
Protocol violation	26	2.3
Total discontinued	483*	42.3
Total entered	1143**	100.0

*Table 8 shows 21 discontinuations at cycle 11 ; this figure should be 20. It also shows 11 discontinuations at cycle 13; this figure should be 10. The figure of 483 is correct.
** 1226 subjects enrolled. The difference between 1226 and 1143, the "total entered" in Table 8 is 83 subjects. In Table 8 in the submission, there is a superscript "b" after the heading "Number of subjects entered", however no corresponding footnote appears. The text (p. 120) states that "the cycle of discontinuation could not be determined for a total of 83 subjects who returned no diaries". It is assumed that these 83 subjects have been omitted from Table 8.

Reviewer's comment:
The pattern of discontinuations at 13 cycles shows nothing unexpected for an OC study.

4.8 Compliance

Women were to record the date and hour of pill taking on their diaries. In the first cycle, 25.3% of subjects forgot to take at least one pill. This dropped to 15.5% by the 18th cycle. One hundred ninety-six (16%) of 1226 volunteers discontinued due to either non-compliance or protocol violations.

Reviewer's comment:
This level of non-compliance is not unexpected in an OC study. Of the in-study pregnancies, only three involved non-compliance.

4.9 Baseline characteristics

The study population was 90% Caucasian and had an average age of 28.3 and BMI of 23.5 kg/m². Sixty-five per cent were nulliparous, 86% smoked three or fewer cigarettes per day, and the average mean coital frequency was about 9.2 acts per month. There were no important differences between Starters and Switchers except in previous contraceptive use. A larger proportion of Starters reported having used barrier methods in the past (95.6% vs 74.4%, respectively). However, 85.3% of Starters had used OCS at some point in the past.

4.10 Efficacy analyses

Pregnancy was suspected or confirmed in 77 volunteers. Of these, pregnancy was confirmed in 45; 11 during study drug administration, 9 prior to start of study drug, and 25 after discontinuation of study drug.

Pregnancies conceived while on study drug

The 11 pregnancies occurred at 11 different sites. The day of study drug administration ranged from (cycle 1 to cycle 15). Two pregnancies occurred in cycles 1-2. The remainder occurred in cycles 6-15.

> **Reviewer's comment:**
> **This pattern is somewhat unexpected. It is more common to see most pregnancies occurring earlier in the study when women are learning to use OCs and when the most fertile women may conceive.**

Three of the 11 reported having taken their pills incorrectly in the cycle in which they conceived. Subject missed her pill on days 1, 5, 6, and 7 of Cycle 10 and conceived on day 14. Subject missed pills on days 1-4 of Cycle 7 and conceived on day 13. Subject missed her pill on day 8 in Cycle 8 although she took it on day 9 (with her day 9 pill). She conceived on day 9. The remaining eight pregnant volunteers reported having taken all their pills in time.

> **Reviewer's comment:**
> **It was hoped that the addition of five days of EE 10 mcg at the end of each pack would make this OC more forgiving of failure to take the first pill(s) in a pack. The fact that two of the 11 pregnancies were in women who missed pills early in the pack might suggest otherwise. However, it is accepted that missing pills early in the pack is the most risky time to miss them and thus the fact that there were two such women in this study is expected. To determine whether this OC is more forgiving of this type of non-compliance would require a comparative study in which the pregnancy rate among such women could be compared. The sponsor has not done such a study and it is not required since the sponsor is not making a claim in this regard.**

Pregnancies conceived prior to administration of study drug

Nine women were reported as conceiving prior to taking study drug. Of these, six returned all study medication and thus there is no question that they conceived prior to starting the drug. The remaining three are included in the All Subjects Treated Group. (This group included all women who were dispensed study drug and did not return it all. It differs from the Intent-to-treat group which includes all women who took study drug and provided some diary information.).

Reviewer's comment:
Of the three subjects who did not return all study drug, CRFs are provided only for Subject who enrolled on 2/2/94. Her LMP was 1/17/94. She was on Orthocept through 2/12/94. She started study drug on 2/13/94 and took her last pill on 5/3/94. She had no menses while on study drug. An ultrasound on 5/4/94 was consistent with a conception date of 1/30/94. She discontinued on 5/3/94 for pregnancy.

Page 156, vol. 39 states that Subject 'called the site and said she experienced amenorrhea and ultimately was pregnant". Subject "became pregnant prior to taking study drug (positive home pregnancy test)". In both cases no study drug was reported to have been taken although none was returned.

Pregnancies conceived after discontinuation of study drug

Twenty-five subjects were determined to be pregnant but their date of conception was after the last tablet was taken. The number of days after discontinuation when conception occurred was known in twenty subjects and ranged from days, with an average of 46.7 days.

Reviewer's comment:
CRFs from the 9 subjects conceiving 30 days or less after the last day of study drug administration and the 5 subjects for whom the time between last dose and conception was unknown were reviewed. Of these 14 patients, 13 had a menses at the end of the last cycle of pills taken. Of these 13, 8 also had ultrasound reports which placed the date of conception after the date of last study drug administration. Thus there is only one patient whose date of conception is not clearly after study drug was stopped.

Subject was enrolled and given three packs on 3/9/94. She took her first dose on 3/20/94. Diary cards for cycles 1 and 2 were returned at her visit on 6/1/94, which was in the middle of her third cycle. At that visit, she was dispensed three more packs. She was seen again on 8/25/94, at which time her diary card for cycle 3 was returned. That cycle ended on 6/11/94. No other diary cards were ever returned. The patient was given three more packs at her August visit. A pregnancy test was negative at that visit, ruling out a conception earlier than 8/15/94. The patient was scheduled to return in November, but apparently didn't show and was considered lost to follow-up on 11/28/94. The site became aware of the subject's pregnancy on 3/6/95 at which time they were told it had ended in a spontaneous abortion on 3/3/95. No other information on this pregnancy is available. It is unclear when this patient stopped study drug, although if she took all the pills she had been given, her last dose would have been on 11/19/94. It is unknown how advanced her pregnancy was at the time of the spontaneous abortion on 3/3/95. However, since the site performed a pregnancy test at the patient's last visit before she was lost to follow-up, it is not justified to include her as a study pregnancy.

Pregnancies suspected but not confirmed

Pregnancy was suspected in thirty-two additional subjects, but a pregnancy test was negative.

Reviewer's comment:
The nine volumes containing printouts for all these subjects were reviewed. The circumstances surrounding the latest pregnancy test for each subject were evaluated.

In 8 cases, the test was done at least ten days after the last active pill was taken.

In 17 cases, there was a menses during the last seven days of the pack preceding the pregnancy test and the during the pack being taken at the time of the pregnancy test and no pills were missed in either pack. It is unclear why the test was done. In many cases, the test was done at the end of the last pack although this was not a protocol requirement.

In 3 cases the test was done because there had been no withdrawal bleed in either that cycle or in the cycle before. In these cases, the cycle in which testing occurred was not the last cycle taken and subsequent cycles had withdrawal bleeds.

In 3 cases, the test was done during the last pack because of failure of withdrawal bleed or mistiming of the withdrawal bleed in previous cycles. In all three cases, there was no bleeding in week four of the last cycle (in which the test was done). One could argue that pregnancy had not been adequately ruled out in these subjects, but the history of failed withdrawal bleeds or mistimed withdrawal bleeds makes pregnancy an unlikely cause. Details are as follows.

Subject took three packs of pills. She missed no pills in any of the packs and had no withdrawal bleed after any pack. A pregnancy test was done on day 9 of her third pack and was negative.

Subject completed 18 cycles. She had no withdrawal bleed in cycles 10, 17, and 18. A pregnancy test on day 16 of cycle 18 was negative.

Subject completed 18 cycles. In cycle 15, she had her withdrawal bleed during the third week instead of the fourth. This occurred in cycles 16, 17, and 18 also. A pregnancy test done on day 5 of Cycle 18 was negative. During cycle 18, she had spotting on days 15, 16, and 17. No other tests were done after the one on day 5.

There is only one case in which pregnancy was not adequately ruled out. Subject completed 18 cycles. Pregnancy tests were done on day 18 of cycle 3, day 20 of cycle 6, day 20 of cycle 9, day 20 of cycle 12, and day 17 of cycle 15 despite there having been no missed pills and no failed withdrawal bleed. A pregnancy test was also done on day 20 of cycle 18. There was no withdrawal bleed in that cycle, although there was one in Cycle 17. No pregnancy tests were done after the one on day 20 in cycle 18. The only other cycle in which there was no withdrawal bleed was cycle 1.

Pearl index and life table pregnancy rate

The Pearl rate using all 14050 cycles of exposure is 1.11 pregnancies per 100 woman-years. The life table rate for the first 13 cycles happens to also be 1.11.

Reviewer's comment:
Adding Subject (the subject above with a negative pregnancy test but an inadequate evaluation) to the in-study pregnancies increases the Pearl Index from 1.11 to 1.21. However, adding her would establish a precedence of considering such patients pregnant on study drug, which does not seem justified. There are no other pregnancies that should be added into the calculation.

4.11 Safety analyses

Safety parameters included AEs and discontinuations due to AEs, changes in physical exam and lab values, and pregnancy outcomes.

Adverse experiences:

Of the 1226 subjects in the All-Subjects-Treated group, 902 (73.6%) reported at least one AE (75.8% of Switchers and 71.1% of Starters). Five hundred thirty-eight (43.9%) reported an AE related to study drug (45.2% of Switchers and 42.4% of Starters).

Serious AEs (SAEs)

Twenty-nine subjects (2.4%) reported a total of 31 serious AE (2.3% of Switchers and 2.4% of Starters). Two SAEs (one case of depression and one case of cholecystitis) were considered by the investigator to be possibly related to the study drug. There were no deaths, myocardial infarctions, pulmonary emboli, strokes, or deep vein thromboses. SAEs are tabulated on the next page (from Table 32, pp. 200-203, vol. 39).

Serious AEs

Related to study drug*	
Reproductive tract	Other
None	Two: Depression Cholecystitis
Not related to study drug	
Reproductive tract	Other
Nine subjects reporting ten SAEs: Uterine fibroid Uterine fibroid** Endometriosis (not found) Endometriosis (not found) Endometriosis and pelvic pain PID Menorrhagia Ectopic pregnancy** Tubal ligation**	20 subjects reporting 20 SAEs (Subjects also reported SAEs in the reproductive tract) Suicide attempt Syncope Cholelithiasis Cholecystitis Appendectomy Appendicitis Appendicitis Sinusitis Sinusitis Anterior cruciate tear Meniscus tear Synovial impingement, knee Chondromalacia patella Wrist fracture Ganglion Lacerated ulnar nerve Breast reduction Lymphoma Viral infection Pharyngitis

* Possibly, probably, or definitely related
** Post-treatment AEs

Reviewer's comment:
The report states that there were 29 subjects who reported a total of 31 SAEs. Table 32 shows 29 subjects reporting 32 SAEs. This discrepancy is not of clinical relevance.
The SAEs seen in this study do not suggest a safety profile different form other OCs.

Non-serious AEs

The system-organ class with the greatest number of non-serious AEs related to study drug was the reproductive tract. Within this class, the most common study drug related AEs were intermenstrual bleeding (7.3% of subjects), breast pain (4.6% of subjects), and dysmenorrhea and menstrual disorder (4.2% of subjects each). Moniliasis was the most common reproductive tract AE not related to study drug, reported by 6.7% of subjects. (In an additional 1.7% of subjects it was reported as drug-related.)

The system-organ class with the next highest incidence of non-serious drug-related AEs was the Central and Peripheral Nervous System, in which headache was the most common AE occurring in 8.5% of subjects (compared with 64.2% in the Desogen NDA). The Metabolic and Endocrine System had the next highest number of drug-related AEs with the most common being weight gain (5.8% of subjects).

Headache was the most frequently reported AE, *disregarding* relatedness to study drug, occurring in 17.9% of subjects. This was followed by upper respiratory tract infection at 15.7% of subject and sinusitis at 11.3%. There was no pattern in any of these three over time. The only frequent AE that changed over time was weight gain which increased from 1.7% of subjects in cycle 1 to 6.0% in cycle 12. The mean change in body weight among all subjects was 1.5 kg (3.3 pounds); the mean change in BMI was 0.5 kg/m^2.

Discontinuations due to AEs

One hundred forty nine subjects (12.2% of 1226 total) discontinued due to an AE (10.5% of Switchers and 14.0% of Starters). Discontinuations for AEs are tabulated on the next page (from Table 33, pp. 206-227, Vol. 39).

Discontinuations due to AEs

	Related to study drug*	
	Reproductive tract	Other
Serious AEs leading to DC	**None**	**None**
AEs that were not serious but led to discontinuation	**Forty-eight** Pregnancy: 10 Menorrhagia: 4 Menstrual disorder: 10 Dysmenorrhea: 3 IMB: 13 Withdrawal bleeding: 2 Amenorrhea: 1 Breast pain: 1 Vaginal candidiasis: 1 Premenstrual tension: 2 Vaginal discomfort: 1	**Eighty-seven**
	Not related to study drug	
	Reproductive tract	Other
Serious AEs leading to DC	**One:** 0902: Uterine fibroid	**One:** 0110: Syncope
AEs that were not serious but led to discontinuation	**Four:** Ovarian pain: 1 Endometrial disorder: 1 In-study pregnancy: 2	**Eight**

* Possibly, probably, or definitely related

Changes in lab values

Five subjects discontinued due to abnormal lab values: one case each of moderate hyperbilirubinemia, mild hyperprolactinemia, mild hypertriglyceridemia, moderately elevated hepatic enzymes, and elevated lactate dehydrogenase. The first three were considered by the investigator to be related to study drug.

Changes in physical exam

There was no significant change in physical exam over time. Hypertension was defined as a systolic blood

pressure of > 140 mm Hg or diastolic > 110 mm Hg with a increase of 10 mm Hg in either on at least two visits or the last visit. Eleven subjects had clinically significant blood pressure changes. Only three subjects discontinued due to hypertension. Overall, a mean change of -0.3 mm Hg a systolic and -0.2 mm Hg diastolic was seen in the 1134 subjects who had both baseline and post-baseline measurements.

Pregnancy outcomes

Of the eleven in-treatment pregnancies, six resulted in uncomplicated live births, three were terminated, one was spontaneously aborted, and one was accidentally interrupted by a scheduled biopsy.

Reviewer's comment:
This pattern of AEs is consistent with that seen with other OCs and does not raise safety concerns regarding this product.

4.12 Cycle control

See Attachment A for definitions of bleeding and spotting. One additional definition is that of Intermenstrual Bleeding (IMB) which combines Breakthrough Bleeding, Breakthrough Spotting, and Breakthrough Bleeding/Spotting.

About 85% of subjects experienced the expected spotting or bleeding during the desogestrel- free period in cycle 3. This dropped to about 80% of subjects by cycle 6 and remained steady through cycle 18. In 8 to 12% of subjects, bleeding began early, before the desogestrel-free period. This pattern held until Cycle 15 when the percent dropped to about 5%. In about 10% of subjects, bleeding continued into the first 2-3 days of the desogestrel-free period. This pattern persisted through cycle 18. Thirty-six subjects (2.9%) discontinued primarily due to menstrual problems.

It is difficult to compare results in this NDA with those in other relevant ones since this study used unusual definitions for bleeding irregularities: Intermenstrual bleeding was any bleeding that occurred during the DSG interval that was neither part of early withdrawal bleeding nor continued withdrawal bleeding. In other studies, breakthrough bleeding/spotting was defined as any occurrence during the 21 days of active pills that was not continuation of withdrawal bleeding but that could include early withdrawal bleeding. The exclusion of this type of bleeding would give the appearance of better bleeding rates for CTR 25 than other products. The sponsor was asked to recalculate bleeding/spotting rates so that they could more easily be compared with other products. Their response was received on November 27, 1997. Results are shown on the next page.

Per cent of cycles in which breakthrough bleeding and/or spotting occurred

Cycle	Preparation						
	Estrostep*	Loestrin*	CTR 25, using same definition as Estrostep& Loestrin	Alesse**	CTR, using same definition as Alesse	Desogen***	CTR 25, using same definition as Desogen
1	58	46	28.9	30.5	28.9	15.4	19.1
3	22	17	23.2	26.6	22.2	9.9	13.9
6	17	13	21.6	25.4	21.2	7.6	14.1
9			17.4	25.2	17.1	5.9	11.5
12			18.8	18.2	18.2	5.9	13.3
18			11.3	27.3	11.6	5.9	9.5

* From Estrostep NDA 20-130. Includes breakthrough bleeding/spotting during the 21 days of active pills that was not continuation of withdrawal bleeding but that could include early withdrawal bleeding.

** From Alesse NDA 20-683. Includes breakthrough bleeding/spotting on days 5-21 inclusive or on days 1-4 inclusive if preceded by 2 consecutive days without bleeding or spotting.

*** Desogen NDA 20-071. Includes any bleeding that occurred during the DSG interval that was neither part of early withdrawal bleeding nor continued withdrawal bleeding.

Reviewer's comment:
Although a better comparison would be afforded by a comparative study, these figures suggest that CTR 25 causes about the same incidence of breakthrough bleeding/spotting as the other 20 mcg EE pills, and more than Desogen which contains 30 mcg EE. The label does not make the claim of better cycle control, however.

4.13 Substudies

Substudy: Endometrial histology

The objective of this study was to assess the effect of CTR 25 on endometrial histology in 40 subjects (Starters) over 13 months at three centers. Biopsies were to be done as follows:

- On or near the baseline visit (approximately 7 days before an expected menses)
- Cycle 13 - between days 18 and 21
- Cycle 14 - between days 1 and 4

Biopsies were read at a central lab and could be classified as any of the following:

- Atrophic
- Inactive
- Weakly proliferative
- Normally proliferative
- Secretory
- Menstrual
- Late menstrual
- Hyperplasia (simple or complex) without cytological atypia
- Hyperplasia with cytological atypia
- Adenocarcinoma
- Other neoplasia
- Sample insufficient

The baseline characteristics of the subset were approximately the same as for the main study.

Reviewer's comment:
Individual records of the subjects in the endometrial biopsy subset were reviewed and double-checked with respect to dates of biopsies, results, and time in cycle when performed (vols. 106, 107, 114, 115, 135, and 136). Results are presented below. Cycles which do not contribute to the objective of assessing "the effects of CTR 25 on endometrial morphology over the course of 13 consecutive cycles" (p. 62, vol. 43) are shaded.

Subject #	Baseline (7 days before menses)		Cycle 13 (days 18-21)		Cycle 14 (days 1-4)	
	Day of cycle	Result	Day of cycle	Result	Day of cycle	Result
14 subjects biopsied at correct time in Cycles 13 and 14:						
	8	normal prolif	day 19, cycle 13	normal prolif	day 2, cycle 14	normal prolif
	8	normal prolif	day 18, cycle 13	secretory	day 2, cycle 14	normal prolif
	14	inactive	day 18, cycle 13	inactive	day 4, cycle 14	late menstrual
	18	normal prolif	day 20, cycle 13	secretory	day 2, cycle 14	normal prolif
	11	normal prolif	day 18, cycle 13	secretory	day 3, cycle 14	normal prolif
	15	normal prolif	day 18, cycle 13	secretory	day 3, cycle 14	late menstrual
	16	normal prolif	day 18, cycle 13	late menstrual	day 3, cycle 14	normal prolif
	12	normal prolif	day 20, cycle 13	inactive	day 3, cycle 14	normal prolif
	24	secretory	day 20, cycle 13	secretory	day 3, cycle 14	normal prolif
	22	secretory	day 20, cycle 13	secretory	day 2, cycle 14	normal prolif
	18	secretory	day 18, cycle 13	secretory	day 2, cycle 14	normal prolif
	17	normal prolif	day 20, cycle 13	secretory	day 3, cycle 14	normal prolif

	18	secretory	day 20, cycle 13	secretory	day 4, cycle 14	normal prolif
	18	normal prolif	day 19, cycle 13	late menstrual	day 2, cycle 14	late menstrual
1 subject biopsied in cycles 13 and 15						
	29	normal prolif	day 19, cycle 13	late menstrual	day 3, cycle 15	normal prolif
1 subject biopsied in cycle 13 but not 14						
	19	late menstrual	day 20, cycle 13	normal prolif		
1 subject biopsied in cycle 13 (at wrong time) but not 14						
	14	secretory	day 11, cycle 13	other neoplasia - immature placenta*		
1 subject biopsied in cycle 13 and 14 but at incorrect time in cycle 13						
	21	secretory	day 11, cycle 13	secretory	day 2, cycle 14	late menstrual
1 subject biopsied in cycle 14 and 15						
	26	secretory	day 17, cycle 14	inactive	day 24, cycle 15	secretory
7 subjects biopsied earlier than cycle 13 only						
	17	normal prolif	10 days after last pill which was taken on day 28 of cycle 1	normal prolif		
	22	secretory	13 days after last pill which was taken on day 18 of cycle 6	normal prolif		
	17	late menstrual	1 day after last pill which was taken on day 18 of cycle 6	normal prolif		
	10	normal prolif	day 12, cycle 7	normal prolif		
	25	secretory	31 days after last pill which was taken on day 28 of cycle 9	normal prolif		
	19	secretory	17 days after last pill which was taken on day 28 of cycle 9	secretory		
	27	secretory	5 days after last pill which was taken on day 28 of cycle 12	normal prolif		
13 subjects with baseline biopsies only erroneously enrolled in this subset)						
	24	secretory				
	19	secretory				

	22	secretory				
	14	secretory				
	24	secretory				
	18	late menstrual				
	24	secretory				
	12	normal prolif				
	20	secretory				
	-11**	secretory				
	26	secretory				
	28***	secretory				
	16	normal prolif				

Note: Subjects were in the subset but had no biopsies performed.
* Subject was pregnant and subsequently underwent a spontaneous abortion
** Subject had an LMP of 2/25 recorded at screening but a screening biopsy dated 2/14
*** Subject had a baseline biopsy but was enrolled in another subset.

Reviewer's comment:
Only 14 of the intended 40 subjects were biopsied at the correct time points in both cycle 13 and cycle 14. Additional subjects contributed data which are considered relevant to the study objective:

- **was biopsied in cycles 13 and 15; her cycle 15 data are considered analogous to cycle 14 data from other subjects.**
- **was biopsied at the correct time in cycle 13 but not at all in subsequent cycles. Her data from cycle 13 are considered relevant.**
- **was biopsied at the wrong time in cycle 13 but her data are considered relevant since timing in cycle 13 is not as critical as that in cycle 14 (timing in cycle 14 is aimed at assessing the presence of hyperplasia immediately after the EE-alone pills)**
- **was biopsied at the incorrect time in cycle 13 but the correct time in cycle 14. Both cycles are considered relevant.**
- **was biopsied late in cycles 14 and 15; both are relevant to the cycle 13 data.**

Thus there are 20 biopsies from cycle 13 (4 done at the incorrect time) and 16 biopsies from cycle 14 (one of which was really taken in cycle 15). This falls far short of the intended 40 biopsies at each time point.

These data also indicate that the Ns in Table 3 on page 72 of volume 43 are incorrect.

	N from submission	N from review
Baseline to cycle 13	22	20
Cycle 13 to cycle 14	17	16
Baseline to cycle 14	4	0

There were no cases of hyperplasia seen, so the issue is not one of misclassifying significant endpoints. Rather it is one of whether the endpoint in question was sought in a sufficient number of patients.

The sequential pills that were associated with an increased risk of endometrial cancer contained 100 mcg of ethinyl estradiol and were taken for 15-16 days for a total monthly dose of 1500-1600 mcg of unopposed estrogen. This was followed by five days of opposed estrogen. CTR 25 exposes women to five days or a total of 50 mcg per month of unopposed estrogen and 21 days or a total of 420 mcg of opposed estrogen per month. The theoretical risk of hyperplasia and endometrial cancer in users of CTR 25 is extremely small, but this study was completely inadequate to evaluate this risk. It is recommended that a study to better assess the risk of hyperplasia in women who complete 12 cycles plus 4 days and undergo endometrial biopsy at baseline and during days 1-4 of cycle 13 be made a Phase IV requirement for approval.

Substudy: Lipid profile:

The objective of this substudy was to evaluate the effect of CTR 25 on fasting lipid levels (total triglycerides, total cholesterol, HDL-C, HDL_2-C, HDL_3-C, LDL-C, VLDL-C, and Lp(a)) in 100 patients (Starters) at 7 sites at baseline, cycle 3, and cycle 6. It was expected that HDL-C would increase, there would be a nominal effect on LDL-C, and no effect on HDL_2-C.

Ninety-seven subjects enrolled. Ninety-three took at least one dose of study medication. Baseline characteristics did not differ in any important way from the main study population. There was a mean increase in triglycerides of 55.0% at 3 months and 60.1 at 6 months. Cholesterol rose 4.8% at 3 months and 9.8% at 6 months. HDL-C rose 10.0% at 3 months and 15.1% at 6 months. HDL_2-C rose 16.9% at 3 months and 24.5% at 6 months. HDL_3-C rose 8.9% at 3 months and 12.9% at 6 months. LDL-C fell 2.6% at 3 months and rose 4.5% at 6 months. VLDL-C rose 58.0% at 3 months and 52.7% at 6 months. Lp(a) rose 5.7% at 3 months and 0.6% at 6 months.

The mean observed values for each parameter were within the normal range. The increase in HDL_2-C was unexpected and probably a favorable effect. Overall, these resulted do not suggest a deleterious effect on lipids.

Substudy: Endocrine profile

The objective of this substudy was to evaluate the effect of CTR 25 on fasting levels of FSH, LH, prolactin, progesterone, 17-beta estradiol, total T_3 total T_4, TBG, cortisol, and CBG in 50 patients (Starters) at 5 sites at baseline, cycle 3, and cycle 6 between day 15 and day 21.

Sixty-four subjects enrolled. Sixty took at least one dose of study medication. Baseline characteristics did not differ in any important way from the main study population. The was a mean decrease in FSH of 15.9% at 3 months and 16.3 at 6 months. LH rose 16.3% at 3 months and fell 24.9% at 6 months. Prolactin rose 30.5% at 3 months and 12.0% at 6 months. Progesterone fell 58.8 % at 3 months and 64.1% at 6 months. Estradiol double antibody fell 56.6% at 3 months and 81.3% at 6 months. Total T_3 rose 33.2% at 3 months and 30.4% at 6 months. Total T_4 rose 58.1% at 3 months and 52.2% at 6 months. TBG rose 69.1% at 3 months and 60. 0% at 6 months. Cortisol went up 175.1% at 3 months and 1743.5 at 6 months. CBG rose 70.7% at 3 months and 64.7% at 6 months. The mean observed values for each parameter were within the normal range with the exception of cortisol and CBG levels, which were not felt to be clinically relevant. All these results were expected given that the study drug shows high progestational activity.

Substudy: Ophthalmology

The objective of this substudy was to evaluate the effect of CTR 25 on ocular complaints, visual acuity, refraction, gross external examination, slit lamp examination, lens examination, and ophthalmoscopy in sixty patients (Starters) at baseline and cycle 13.

Fifty-five subjects enrolled. Fifty-five took at least one dose of study medication. Women with certain pre-existing conditions of the eye were excluded. Baseline characteristics did not differ in any important way from the main study population.

Two subjects had findings at the final examination that were not present at baseline: One subject had a 1.5 disc diameter of pigmentation below the macula of the right eye at the final examination. One subject had a superficial pannus due to contact lenses in both eyes at the final examination. Only 36 subjects had acuity readings at baseline and 13 months. Of these, 28 did not change. Two subjects went from 20/25 to 20/20 and one from 20/30 to 20/25. One subject went from 20/15 to 20/25 and four subjects went from 20/20 to 20/25.

Substudy: Hemostasis and fibrinolysis

The objective of this substudy was to evaluate the effect of CTR 25 on Prothrombin time, APPT, fibrinogen, D-dimer (fibrin split products), plasminogen activator inhibiter 1 and total, antithrombin III, Factor VII, plasminogen, and fibrin degradation products in 100 patients (Starters) at 10 sites at baseline, cycle 3, and cycle 6 between day 15 and day 21.

Ninety-nine subjects enrolled. Ninety-eight took at least one dose of study medication. Baseline characteristics did not differ in any important way from the main study population.

Values for D-dimer were above normal at baseline (mean of 611.7 ng/ml with an upper limit of normal of <400 ng/ml.) The mean increased to 884.2 ng/ml at cycle 3 and fell to 595.7 ng/ml at cycle 6. Additional information supplied by fax from the sponsor on 1/15/98 showed that the women who discontinued after

cycle 3 had values of D-dimer at cycle 3 that were higher than at baseline. Women who completed 6 cycles had values that, on average, decreased at cycle 3 compared with baseline and at cycle 6 compared with cycle 3. The same pattern was seen when women ta site 8, a site with many outlying values, were excluded. The percent change from baseline was significant at $p < 0.05$ when cycle 3 was compared with baseline, and when cycle 6 was compared with baseline for all sites excluding site 8. The percent change in mean absolute values was not significant.

Of the 15 women who discontinued after cycle 3, only three discontinued due to an adverse experience (subjects reporting abnormal crying, acne, and palpitations respectively).

Reviewer's comment:
A recent article on the predictive value of D-dimer[ref 6] in DVT concluded that values of less than 2000 ng/ml were exclusionary for a diagnosis of DVT. The article also cautions, however, that here is a lack of standardization between test methods. In this study, there were six women with values over 2000 ng/ml at baseline. All completed 6 cycles and none had values over this level at cycle 6. An additional four subjects had values less than 2000 ng/ml at baseline but values over 2000 ng/ml at cycle 3. Of these, two discontinued after cycle 3 and two had values less than 400 ng/ml at cycle 6.

Mean values for Factor VII were 148.2% at baseline, 162.3% at cycle 3, and 135.1% at cycle 6 (normal range 65-135%). Additional information supplied by fax from the sponsor on 1/15/98 showed that the women who discontinued after cycle 3 had values of Factor VII at cycle 3 that were lower than those of women who completed 6 cycles. The percent change from baseline was significant at $p < 0.05$ when cycle 3 was compared with baseline for women completing only 3 cycles and when cycle 6 was compared with baseline for women completing 6 cycle. The percent change in mean absolute values was not significant.

All other parameters were within the normal range at baseline and during test cycles.

Previous studies[refs 5,6] comparing Mercilon and Marvelon have shown that D-dimer fibrin degradation products, prothrombin fragments 1 and 2, antithrombin III, protein S, and Protein C levels change during administration of either pill, in a pattern that favors thrombus formation. In one study[ref 7], all values stayed within the normal range except for F1+2. However, the 30 mcg formulation caused significantly greater changes in D-dimer, ATIII, and Protein S.

Reviewer's comment:
The results in this subset probably are not cause for concern, especially since there were no AEs related to thrombus formation. However, I have discussed the results with Kurt Sizer, M.D., a reviewer in the Division of Gastrointestinal and Coagulation Drug Products, who recommends an official consult with his division to further evaluate the significance of the D-dimer and Factor VII results.

Substudy: carbohydrate metabolism

The objective of this substudy was to evaluate the effect of CTR 25 on the three-hour glucose tolerance test in 30 patients (Starters) at one site at baseline, cycle 3, and cycle 6 between day 15 and day 21.

Thirty-two subjects enrolled. Thirty took at least one dose of study medication. Baseline characteristics did not

differ in any important way from the main study population. The mean AUC for glucose increased from 269.8 hr-mg/dL at baseline to 290.6 at 3 months and 289.9 at 6 months, an increase of about 7.5%. The mean AUC for insulin increased from 128.3 hr-uIU/mL at baseline to 171.4 at cycle 3 and 179.2 at cycle 6, an increase of about 37%. At 3 hours after the glucose challenge, the mean glucose level was 71 mg/dL at baseline, and 74.1 at cycle 6, and difference of 4.4%. The mean difference in insulin levels was 8.3% at cycle 6.

These results are not unexpected in OC users since OCs are known to impair glucose tolerance slightly in some users.

Subset study: pharmacokinetics

(Please see biopharm review.)

4.14 Reviewer's assessment of safety and efficacy

The submitted data provide adequate assurance that CTR is safe and effective for marketing. It does not appear to offer advantages over Desogen or other OCs containing 20 mcg EE. The risk of endometrial hyperplasia has not been adequately addressed by Substudy C and should be further studied in a study, but this risk is very small and is not a sufficient reason to withhold approval.

5. PROTOCOL 31904: a RANDOMIZED, GROUP COMPARATIVE, DOUBLE BLIND, PLACEBO-CONTROLLED STUDY OF THE PHARMACODYNAMIC EFFECT OF 10 MCG ETHINYL ESTRADIOL IN THE TABLET-FREE PERIOD OF a LOW-DOSE ORAL CONTRACEPTIVE (VOL 27)

The objective of this study was to determine the effect of adding 5 days of EE 10 mcg on days 24-28 to the formulation consisting of 150 mcg DSG and 20 mcg EE on days 1-21. Endpoints included ultrasound, estradiol, progesterone, FSH, LH, EE, and vaginal bleeding patterns. It was done at one center in the UK.

Fifty women were randomized to receive either 2 placebo tablets followed by 5 tablets of 10 mcg EE or seven placebo tablets during days 22-28. During the remainder of the cycle, each woman took 150 mcg DSG and 20 mcg EE. They were followed for three cycles with endpoints being follicular development as seen on ultrasound and bleeding patterns recorded on diaries. Ultrasound was performed twice a week starting on day 22-28 of cycle 1. In addition, blood was drawn for 17-beta estradiol at the time of each ultrasound. Progesterone and estradiol levels were also drawn on days 4, 7, and 10 post-ovulation. a subset of 5 volunteers in each group were tested for FSH, LH, estradiol, and EE on days 22-28 of cycle 2 and on day 1 of cycle 3.

Ultrasound results (from pages 40-42, volume 27):

Largest follicle:	Group receiving 10 mcg ethinyl estradiol during days 24-28			
	Screening	Cycle 1	Cycle 2	Cycle 3
Foll ≥ 15 mm, rupture	22			
Foll ≥ 15 mm, decr size	2			
Foll 15-30 mm, no rupture	1		1	2
Foll > 30 mm, no rupture				
Foll < 15 mm		12	15	12
Unclassifiable				
No follicle		9	4	7
Total	25	21	20	21
Largest follicle:	Placebo group			
	Screening	Cycle 1	Cycle 2	Cycle 3
Foll ≥ 15 mm, rupture	25		1	
Foll ≥ 15 mm, decr size				1
Foll 15-30 mm, no rupture		1	4	4
Foll > 30 mm, no rupture			1	1
Foll < 15 mm	2	18	13	12
Unclassifiable				
No follicle		4	2	5
Total	27	23	21	23

Reviewer's comment:
There was no statistically significant difference between the two groups in cycle 3, comparing the incidence of follicles ≥ 15 mm with follicles < 15 mm ($p = 0.2451$).

Progesterone levels were < 10 nmol/l in all subjects with the exception of three in the placebo group. Two of these had P levels of 27 and 28 nmol/l between days 1 and 21 in cycle 2 and the third had a value of 28 nmol/l between days 1 and 21 in cycle 3.

Estradiol levels were < 100 pmol/l in most subjects in all cycles, with the exception of cycle 1 in which 10 placebo users had values < 100 pmol/l and 13 had higher values. There were levels as high as 894 pmol/l in the CTR 25 group and 1221 pmol/l in the placebo group.

There was a suggestion of lower levels of FSH and LH among CTR 25 users, but the sample size was too small to draw conclusions.
Subjects in the CTR 25 group experienced more bleeding/spotting episodes than did placebo users in the 77-day reference period (4.3 vs 3.8). However, the bleeding/spotting episodes were shorter for CTR users than placebo users (5.5 vs 7.3 days) and CTR 25 users experienced fewer bleeding or spotting days altogether (22.1 vs 24.0). The mean number of bleeding days was slightly higher in the placebo group (17.3 vs 13.3) while the mean number of spotting days was higher in the CTR 25 group (8.8 vs 6.7).

Reviewer's comment:
This study shows a nonsignificant difference in follicular development that favors CTR 25, as manifested by ultrasound results. CTR 25 users experienced more bleeding/spotting episodes but they were shorter and consisted of more spotting days than among placebo users.

6. PROTOCOL 39801: a RANDOMIZED, MULTI CENTER COMPARATIVE DOUBLE BLIND PLACEBO CONTROLLED STUDY OF THE EFFECT ON THE VAGINAL BLEEDING PATTERN OF 10 MCG ETHINYL ESTRADIOL IN THE TABLET-FREE PERIOD OF a LOW DOSE ORAL CONTRACEPTIVE (VOL 60-61)

This study enrolled 200 women in each of two groups at ten European centers. Both groups received 21 days of desogestrel 150 mcg. The CTR 25 group received two days of placebo followed by 5 days of EE 10 mcg on cycle days 24-28. The placebo group received seven placebo tablets from days 22-28. Randomization was stratified according to Starter vs Switcher status. Women were followed for six cycles.

The endpoint was bleeding patterns as recorded on daily diaries. Spotting was defined as that requiring not more than one tampon/pad, while bleeding was defined as that requiring more than one.

One hundred ninety-nine women received treatment in the placebo group and 211 did in the CTR 25 group. One hundred fifty-seven women completed the study in both groups. Thirty five per cent of placebo users were Starters while 38% of women in the CTR 25 group were. Nine hundred forty-four cycles were included in the ITT analysis for the placebo group and 943 for the treatment group.

Women were on average 27 years old, had a BMI of 21.7 and had experienced 0.9 pregnancies.

Breakthrough bleeding and/or spotting occurred in 23.2% of women in the placebo group in the first cycle, compared with 20.5% in the CTR 25 group. In cycles 2 through 6, however, breakthrough bleeding and/or spotting occurred in a greater proportion of patients in the CTR 25 group, due mostly to differences in spotting. Overall, breakthrough bleeding and/or spotting occurred in 15.9% of CTR 25 cycles compared with 12.4% of placebo cycles. The absence of withdrawal bleeding was somewhat higher in the CTR 25 group also. The duration of bleeding was similar in both groups.

There were no serious AEs related to study drug.

Reviewer's comment:
The conclusion of the study report states that "...this study showed only a slight difference in cycle control, mainly in the occurrence of breakthrough spotting only, in favor of the CTR 25 (placebo) group vs the CTR 25 (EE) group." This study failed to show that the addition of

the 10 mcg EE improves overall bleeding patterns.

7. Reviewer's assessment of safety and efficacy

The goal of development of this product was to provide a smaller monthly dose of EE compared with Desogen to improve safety, but without compromising efficacy and cycle control. The dose of EE was lowered from 30 mcg to 20 mcg on days 1-21 and increased from 0 to 10 mcg on days 24-28.

While the product appears effective, the studies failed to show that the addition of EE on days 24-28 improves follicular suppression or cycle control compared with not administering EE during this time. The risk of endometrial hyperplasia that theoretically ensues from the addition of five days of unopposed estrogen has not been adequately evaluated.

This formulation offers no advantages over existing ones, but shows adequate efficacy and safety for approval, other than the concern regarding endometrial hyperplasia. In studies of this size one is not likely to see a difference in safety parameters such as DVT, stroke, or MI which have been the subject of concern with regard to this progestin. A recent review of this issue by the World Health Organization concluded that there may be a slightly increased risk of DVT with desogestrel; this has been incorporated into the revised class labeling for OCs.

8. Comments on proposed labeling

9. Recommendations for regulatory action

An official consult with the Division of Gastrointestinal and Coagulation Drug Products to further evaluate the significance of the D-dimer and Factor VII results is recommended.

Unless this consult suggests otherwise, approval is recommended with the requirement for a

study to better assess the risk of endometrial hyperplasia in women who complete 12 cycles plus 4 days and undergo endometrial biopsy at baseline and during days 1-4 of cycle 13.

/S/

Christine Klein Mauck, M.D., M.P.H.
Medical Officer, DRUDP

Concurrences /S/ 2-18-98

Concurrences:

Heidi Jolson, M.D., M.P.H., Deputy Director, DRUDP

cc: Christina Kish
Lisa Rarick, M.D.
Amit Mitra, Ph.D.
Krishan Raheja, Ph.D.
Angelica Dorantes, Ph.D.
Gary Barnette, Ph.D.
NDA 20-713
Division file
Christine Mauck, M.D., M.P.H.

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1. Akerlund M, Rode A, Westergaard J, Comparative Profiles of reliability, cycle control, and side effects of two oral contraceptive formulations containing 150 mcg desogestrel and either 30 mcg or 20 mcg ethinyl estradiol, Br J Obstet Gynecol, 1993, 100:832-8.

2. Akerlund A, Almstrom e, Hogstedt S, Nabrink M, Oral contraceptive tablets containing 20 and 30 mcg of ethinyl estradiol with 150 mcg desogestrel, Acta Obstet Gynecol, 1994, 74: 136-143.

3. Song S, Jun-Kang C, Pei-Juan Y, Mei-li H, A cross-over study of three oral contraceptives containing ethinyl estradiol and either desogestrel or levonorgestrel, Contraception 1992, 45:523-32.

4. Coenen C, Thomas C, Borm G, Hollanders J, Rolland R, Changes in androgens during treatment with four low-dose contraceptives, Contraception, 1996, 53(3), 171-6.

5. Winkler UH, Holsher T, Schulte H, Zierleyn JP, Collet W, Schindler AE, Ethinylestradiol 20 vs 30 mcg combined with 150 mcg desogestrel: a large comparative study of the effects of two low-dose oral contraceptives on the hemostatic system. Gynecol Endocrine 10 (1996): 265-271.

6. Kozman H, Flemmer MC, Rahnama M, Deep venous thrombosis: prediction by D-dimer? Southern Med J (1997): 90:907-10.

7. Winkler UH, Holscher TSchulte H, Zierleyn JP, Collet W, Schindler AE, Ethinylestradiol 20 vs 30 mcg combined with 150 mcg desogestrel: a large comparative study of the effects of two low-dose oral contraceptives on the hemostatic system. Gynecol Endocrine 10 (1996): 265-271.

ORIGINAL JAN 13 1998

NDA: 20-713

Medical Officer's Review
(120 day safety update)

Date submitted: 8/29/97
Date received: 9/2/97
Date assigned: 9/3/97
MOR completed 1/13/98

Sponsor: Organon Inc.
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Drug:

Generic	Desogestrel/ethinyl estradiol and ethinyl estradiol
Trade:	CTR 25
Chemical:	13-ethyl-11-methylene-18,19-dinor-17 alpha-pregn-4-en-20-yn-17-ol

Route: Oral

Dosage form: Oral tablet

Strength:

Days 1-21:	150 mcg desogestrel/20 mcg ethinyl estradiol
Days 22-23:	placebo
Days 24-28:	10 mcg ethinyl estradiol

Indication: Contraception

This one-volume submission contains the Foreign Postmarketing Surveillance Report of adverse experiences for Mercilon as of January 1, 1997. The first 21 tablets in each Mercilon pack are identical to CTR 25. However, the 21 active tablets are followed by 7 placebo tablets in Mercilon and by 2 placebo then 5 tablets containing 10 mcg EE in CTR 25.

This submission contains all AE reports ever received by Organon for Mercilon world-wide since marketing i 1988. A total of 700 AEs from 16 of the 40 countries in which Mercilon is marketed are included.

There were 225 serious AEs, but only 19 were serious and unexpected. Among the serious AEs, there were 13 deaths, one each due to syncope, MI, cardiac arrest, cerebral vein thrombosis, cerebral artery thrombosis, and mesenteric vein thrombophlebitis, and seven to pulmonary embolism.

Approximately one quarter of all 700 AEs were reproductive tract disorders, mostly pregnancy (146 cases), and another quarter were vascular (extracardiac) disorders, most commonly thrombophlebitis. About 13% were skin and appendage disorders and 11% were platelet, bleeding, and clotting disorders, most commonly pulmonary embolism.

The incidence of venous thromboembolic AE reports is 1.51 per 100,000 woman-years. Annual figures doubled in 1996 compared with 1995, most likely due to the adverse publicity about the risk of thromboembolic events among users of third generation progestins. This compares with an estimated annual

risk of deep vein thrombosis in women taking low dose combined OCs of 4 per 100,000 woman-years. The incidence of cerebrovascular AEs is 0.42 per 100,000 woman-years, which compares favorably with an estimate of 10.1 for previous studies.

Reviewer's comment:
Spontaneous reporting of this kind usually underestimates the actual incidence of an AE. However, given the intense controversy about the risk of thrombosis with this progestin, it is likely that spontaneous reporting approaches the actual incidence rate. These figures do not give rise to concern over the safety of this product.

/S/

Christine Klein Mauck, M.D., M.P.H.
Medical Officer, DRUDP

H Jolson 1/13/98

Concurrences:

Heidi Jolson, M.D., M.P.H., Deputy Director, DRUDP

cc: Christina Kish
Heidi Jolson, M.D., M.P.H.
NDA 20-713
Division file
Christine Mauck, M.D., M.P.H.

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Date NDA submitted: 4/30/97
Date NDA received: 4/30/97

Sponsor: Organon Inc.
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Drug: "CTR 25"
Desogestrel 150 mg/ethinyl estradiol 20 mcg days 1-21
Placebo days 22-23
Ethinyl estradiol 20 mcg alone days 24-28

Proposed indication: Contraception

Related NDAs: NDA 20-071 CTR 04 - marketed product (Desogen)

Background

- Desogestrel is one of three "third generation" progestins developed for OCs (the other two are norgestimate and gestodene).
- Has a high progestational activity, no estrogenic activity and only weak androgenic activity, making it less likely than some other progestins to cause unfavorable effects on lipids.
- Are currently two OCs containing desogestrel on the market, both of which are monophasic and contain 150 mcg desogestrel. Desogen/OrthoCept in the US and Marvelon (approved in 70 countries) contain 30 mcg ethinyl estradiol. Mercilon (approved on 46 countries) contains 20 mcg ethinyl estradiol.
- CTR-25 also contains 150 mcg desogestrel and 20 mcg ethinyl estradiol for 21 days. However the 21 days are followed by 2 placebo tablets and then five tablets containing 10 mcg ethinyl estradiol alone.
- "The primary aim of this regimen is to further suppress ovarian function to the point where contraceptive efficacy is not compromised if a pill is missed at the beginning of the next cycle. The regimen also aims to maintain a pattern of regular menstrual bleeding approximately every 28 days utilizing a reduction in the level of EE as compared with 30 mcg EE-containing oral contraceptives, such as Desogen."
- There is currently only one OC on the market in the US that contains 20 mcg EE (Loestrin1/20).

Regulatory history

IND
Received 8/27/93. Phil Price reviewed proposed pivotal study.

- 2 year open label study of 1200 women, 30-40 sites in US. Up to 18 cycles. 200 to complete 13 cycles. Endpoints: efficacy, bleeding, safety.
- Seven subsets: lipids, endocrine, endometrial morphology, carbohydrate metabolism, steady state PK, hemostasis/fibrinolysis, ophthalmic conditions.
- Issues: exclusion of smokers and antibiotic users, instructions for missed pills - resolved.

Preclinical studies

The non-clinical section of this NDA is included by cross-reference to the same in the Desogen and Tri-Desogen NDAs and IND.

Clinical studies

086-002 A single dose study of the bioavailability of CTR-25 (150 mcg DSG/20 mcg EE tablet) relative to a combination solution

Done in U.S.

086-003 A single dose study of the bioavailability of CTR 25 (10 mcg EE tablet) relative to an EE solution

Done in U.S.

31904 A Randomized, Group Comparative, Double Blind, Placebo-controlled study of the pharmacodynamic effect of 10 ethinyl estradiol in the tablet-free period of a low-dose oral contraceptive

Done in UK
n=47
Endpoints: ovarian function as seen on ultrasound and serum progesterone

39801 A randomized, multicenter comparative double blind placebo controlled study of the effect on the vaginal bleeding of 10 mcg ethinyl estradiol in the tablet-free period of a low dose oral contraceptive

Done in UK
n - 1887, 12 centers
Endpoints: contraception (?) and cycle control
Formulation different from study 086-001

086-001 An open-label multicenter non-comparative safety and efficacy study of the desogestrel containing oral contracept CTR 25

Done in US
n=1250, 33 centers
663 women completed 13 cycles, 14050 women years
45 pregnancies, of which 11 were in study
Pearl = 1.11 if barrier use is excluded, 1.01 if included. Life table = 1.11.
Seven subsets: lipids, endocrine, endometrial morphology, carbohydrate metabolism, steady state PK, hemostasis/fibrinolysis, ophthalmic conditions.

Endometrial morphology subset: - data on baseline to cycle 13 (days 18-31) on 22 patients and on

cycle 13 to cycle 14 (days 1-4) on 17. On baseline to cycle 14 only 4.

Filing issues:

- No rationale for assuming applicability of foreign trial data to US
- No stratified analysis by age and race
- Was asked to submit a discussion of postmarketing surveillance in the context of distribution and usage, to include literature search on Mercilon and all internal reports generated from the spontaneous adverse reaction reports for Mercilon (expected to be about 387) - not included

Ease of review issues:

- Need list of volunteers for whom CRFs are submitted and why
- Want more detailed line listings on pregnancies (date of enrollment, date of first and last drug intake, results and dates of all pregnancy tests, dates of any menses recorded, last day in efficacy analysis, gestational age at pregnancy outcome and at any ultrasounds for which records are available)
- Want more detailed line listings for histology subset (all biopsy results, dates of menses, first and last days of drug intake)

Christine Klein Mauck, M.D., M.P.H.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-713

CHEMISTRY REVIEW(S)

DF

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS - HFD-580
Review of Chemistry, Manufacturing and Controls

MAR 20 1998

NDA #: 20-713
CHEMISTRY REVIEW #: 4 **DATE REVIEWED:** 20-MAR-98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	30-APR-97	30-APR-97	20-MAY-97
Amendment	03-FEB-98	05-FEB-98	12-FEB-98
Amendment	06-MAR-98	09-MAR-98	11-MAR-98
Amendment	12-MAR-98	13-MAR-98	20-MAR-98

NAME & ADDRESS OF SPONSOR: Organon, Inc.
375 Mt. Pleasant Avenue
West Orange, NJ 07052

DRUG PRODUCT NAME:

Proprietary:	Mircette
Nonproprietary/Established/USAN:	Desogestrel (DSG)/Ethinyl Estradiol (EE)
Code Name/#:	CTR 25
Chem.Type/Ther.Class:	3S

PARMACOLOGICAL CATEGORY/INDICATION: Progestin, estrogen/Female oral contraceptive

DOSAGE FORM:	Coated Tablets
STRENGTHS:	150 mg DSG/20 mg EE and 10 mg EE
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	x Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1) Desogestrel: a) 13-Ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-17-ol
b) 18,19-Dinorpregen-4-en-20-yn-17-ol,13-ethyl-11-methylene, (17α)
Molecular formula: $C_{22}H_{30}O$ Molecular weight: 310.48

2) Ethinyl estradiol: a) 19-Nor-17α-pregn-1,3,5(10)-trien-20-yne-3,17-diol
b) 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)
Molecular formula: $C_{20}H_{24}O_2$ Molecular weight: 296.41

CONCLUSIONS & RECOMMENDATIONS:
This review covers the response to the final deficiency in the drug product documented in Chem. Rev. #3. **This NDA is now approvable.**

cc:
Orig. NDA #20-713
HFD-580/Division File
HFD-580/CKish
HFD-580/MRhee/DLin

R/D Init by: 3/20/98
filename: nda20713.4 (doc)

/S/
3/20/98
David T. Lin, Ph.D.
Review Chemist

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS - HFD-580
Review of Chemistry, Manufacturing and Controls

NDA #: 20-713
CHEMISTRY REVIEW #: 3 **DATE REVIEWED:** 27-FEB-98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	30-APR-97	30-APR-97	20-MAY-97
Amendment	03-FEB-98	05-FEB-98	12-FEB-98
Amendment	13-FEB-98	17-FEB-98	25-FEB-98
Amendment	20-FEB-98	21-FEB-98	24-FEB-98
Amendment	25-FEB-98	26-FEB-98	27-FEB-98

NAME & ADDRESS OF SPONSOR: Organon, Inc.
375 Mt. Pleasant Avenue
West Orange, NJ 07052

DRUG PRODUCT NAME:
Proprietary: Desogen-20 (considered unacceptable, new name to be resubmitted)
Nonproprietary/Established/USAN: Desogestrel (DSG)/Ethinyl Estradiol (EE)
Code Name/#: CTR 25
Chem.Type/Ther.Class: 3S

PARMACOLOGICAL CATEGORY/INDICATION: Progestin, estrogen/Female oral contraceptive

DOSAGE FORM: Coated Tablets
STRENGTHS: 150 mg DSG/20 mg EE and 10 mg EE
ROUTE OF ADMINISTRATION: Oral
DISPENSED: __x__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1) Desogestrel: a) 13-Ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-17-ol
b) 18,19-Dinorpregen-4-en-20-yn-17-ol,13-ethyl-11-methylene, (17α)
Molecular formula: $C_{22}H_{30}O$ Molecular weight: 310.48

2) Ethinyl estradiol: a) 19-Nor-17α-pregn-1,3,5(10)-trien-20-yne-3,17-diol
b) 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)
Molecular formula: $C_{20}H_{24}O_2$ Molecular weight: 296.41

CONCLUSIONS & RECOMMENDATIONS:
This review covers the responses to the deficiencies in the drug product documented in Chem. Rev. #2. All the deficiencies have been satisfactorily addressed except for the one issue delineated in the List of Chemistry Deficiencies and Comments, and therefore **this NDA is now approvable pending resolution of the aforementioned issue.** The Nomenclature and Labeling Committee will be consulted when the firm supplies an alternative tradename.

cc:
Orig. NDA #20-713
HFD-580/Division File
HFD-580/CKish
HFD-580/MRhee/DLin

R/D Init by: 3/2/98
filename: nda20713.3 (doc)

/S/
3/2/98
David T. Lin, Ph.D.
Review Chemist

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS - HFD-580
Review of Chemistry, Manufacturing and Controls

NDA #: 20-713
CHEMISTRY REVIEW #: 2 **DATE REVIEWED:** 22-JAN-98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	30-APR-97	30-APR-97	
Amendment	30-SEP-97	01-OCT-97	04-OCT-97
Amendment	31-DEC-97	06-JAN-98	07-JAN-98
Amendment	08-JAN-98	09-JAN-98	13-JAN-98
Amendment	12-JAN-98	12-JAN-98	14-JAN-98

NAME & ADDRESS OF SPONSOR: Organon, Inc.
375 Mt. Pleasant Avenue
West Orange, NJ 07052

DRUG PRODUCT NAME:
Proprietary: Desogen-20 (considered unacceptable, new name to be submitted)
Nonproprietary/Established/USAN: Desogestrel (DSG)/Ethinyl Estradiol (EE)
Code Name/#: CTR 25
Chem.Type/Ther.Class: 3S

PARMACOLOGICAL CATEGORY/INDICATION: Progestin, estrogen/Female oral contraceptive

DOSAGE FORM: Coated Tablets
STRENGTHS: 150 µg DSG/20 µg EE and 10 µg EE
ROUTE OF ADMINISTRATION: Oral
DISPENSED: x Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1) Desogestrel: a) 13-Ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-17-ol
b) 18,19-Dinorpregen-4-en-20-yn-17-ol,13-ethyl-11-methylene, (17α)
Molecular formula: $C_{22}H_{30}O$ Molecular weight: 310.48

2) Ethinyl estradiol: a) 19-Nor-17α-pregn-1,3,5(10)-trien-20-yne-3,17-diol
b) 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)
Molecular formula: $C_{20}H_{24}O_2$ Molecular weight: 296.41

CONCLUSIONS & RECOMMENDATIONS:
This review covers the responses to the deficiencies for the drug substances DMFs and drug product documented in Chem. Rev. #1. It also covers the review of updated stability data on the first three commercial batches of CTR-25 tablets. All the deficiencies have been satisfactorily addressed except for three issues delineated in the List of Chemistry Deficiencies and Comments, and therefore this NDA is now approvable pending resolution of the aforementioned issues. The firm's 24 month stability data appears to support their request for a 36 month expiration date. The Division of Biopharmaceutics has determined that the dissolution specifications (Q= % at min) are satisfactory. The Nomenclature and Labeling Committee will be consulted when the firm supplies a new tradename. EA is still pending.

cc:
Orig. NDA #20-713
HFD-580/Division File
HFD-580/CKish
HFD-580/MRhee/DLin 1/27/98

R/D Init by:
filename: nda20713.2 (doc)

/S/ 1/27/98

David T. Lin, Ph.D.
Review Chemist

revised 1/27/98

Kish

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS - HFD-580
Review of Chemistry, Manufacturing and Controls

SEP 29 1997

NDA #: 20-713
CHEMISTRY REVIEW #: 1 **DATE REVIEWED:** 9-8-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	4-30-97	4-30-97	5-20-97
Amendment	7-3-97		

NAME & ADDRESS OF SPONSOR: Organon, Inc.
375 Mt. Pleasant Avenue
West Orange, NJ 07052

DRUG PRODUCT NAME:

Proprietary:	Desogen-20
Nonproprietary/Established/USAN:	Desogestrel (DSG)/Ethinyl Estradiol (EE)
Code Name/#:	CTR 25
Chem.Type/Ther.Class:	3S

PARMACOLOGICAL CATEGORY/INDICATION: Progestin, estrogen/Female oral contraceptive

DOSAGE FORM:	Coated Tablets
STRENGTHS:	150 µg DSG/20 µg EE and 10 µg EE
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	___x___ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1) Desogestrel: a) 13-Ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-17-ol
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Molecular formula: $C_{22}H_{30}O$ Molecular weight: 310.48

2) Ethinyl estradiol: a) 19-Nor-17α-pregn-1,3,5(10)-trien-20-yne-3,17-diol
b) 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)
Molecular formula: $C_{20}H_{24}O_2$ Molecular weight: 296.41

CONCLUSIONS & RECOMMENDATIONS:

This NDA is not approvable from the standpoint of chemistry and manufacturing controls. The application contains a number of deficiencies delineated in the draft letter, which need to be addressed by the sponsor before approval. Information request letters have also been submitted to the DMF holders. EA and Tradename reviews are pending.

cc:
Orig. NDA #20-713
HFD-580/Division File
HFD-580/CKish
HFD-580/MRhee/DLin

R/D Init by: 9/29/97
filename: nda20713.1 (doc)

/S/ 9/29/97
David T. Lin, Ph.D.
Review Chemist

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-713

PHARMACOLOGY REVIEW(S)

KLSh

NDA 20-713 August 6, 1997 AUG - 6 1997

CTR-25
Organon, Inc
West Orange, NJ

Pharmacology Review of the NDA

Drug: CTR-25 (desogestrel 150 ug plus ethinyl estradiol 20 ug for 21 days and 10 ug ee alone for 5 days.

This NDA cross references the approved NDA 20-071 for desogestrel. There are no pharm/tox issues.

Recommendation: The NDA is approvable for pharm/tox. There are no labeling issues.

/S/

Alex Jordan, PhD 8/6

NDA 20-713
HFD-580

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-713

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Clinical Studies

MAR 18 1998

NDA No:	20-713
Applicant:	Organon Inc.
Name of Drug:	CTR 25 (Desogestrel 150 mg/ethinyl estradiol 20 mcg)
Indication:	Contraception
Documents Reviewed:	Vols 1.1, 1.2, 1.39, 1.49, and 1.60

1. Introduction

The applicant has presented the results of 5 clinical trials (1 uncontrolled clinical study 086001, 3 clinical pharmacology studies - 086002, 086003 and 31904 and 1 other clinical study 39801) to establish the efficacy of CTR 25 for the indication of prevention of pregnancy. CTR 25 is a 28-day oral contraceptive; its regimen consists of 150 mg desogestrel and 20 mcg ethinyl estradiol for 21 days, followed by a placebo for 2 days and 10 mcg ethinyl estradiol for the final 5 days. These tablets are to be taken once a day, at the same time each day, preferably at night. The primary aim of the regimen is to further suppress varian function to the point where contraceptive efficacy is not compromised if a pill is missed at the beginning of the next cycle. This review focuses on study 086001.

2. Uncontrolled Clinical Study - 086001

The objectives of this study were to evaluate the contraceptive efficacy, vaginal bleeding patterns, and safety in 1,200 healthy female subjects over a minimum of 10,000 cycles with at least 200 women completing a minimum of 13 consecutive cycles. This study also evaluates seven subsets for hemostasis and fibrinolysis (100 subjects), ophthalmic condition (60 subjects), lipids profiles (100 subjects), endocrine profiles (50 subjects), endometrial biopsy (40 subjects), carbohydrate metabolism (30 subjects), and steady state pharmacokinetics parameters (18 subjects).

This was an open label, non-comparative efficacy and safety study, conducted in thirty-three centers in the United States. It was desirable that at least half of the study group in each center be recruited from Starters who had not used OCs within 2 months prior to enrollment. The remainder were Switchers who were currently using or who had used a combination progestogen/estrogen oral contraceptive within 2 months prior to study start. Women were followed every three months for 18 cycles.

2.2 Patient Disposition

1250 subjects enrolled

24 never took the study drug. (16 starters, 7 switchers, and 1 subject who was not classified either starter or switcher)

1226 subjects took study drug

585 (48%) were starters contributing 5947.5 cycles of exposure to CTR 25

641 (52%) were switchers contributing 8102.5 cycles of exposure to CTR 25

total of 14049.9 cycles of exposure

Of the 1226 subjects who took the study drug

899 (73.3%) discontinued from the study

126 (10.3%) subjects related to AE

11 (0.9%) subjects of non-drug related reason

118 (9.6%) subjects of reason unknown

14 (1.1%) subjects pregnancy or suspicion thereof

126 (10.3%) subjects non-compliance

208 (17.0%) subjects personal reason

70 (5.7%) subjects protocol violation

226 (18.4%) subjects study close out

327 (26.7%) completed 18 cycles

108 (33%) subjects were starters

219 (67%) subjects were switchers

Of the 1226 subjects, 1143 took the study drug - the Intent-to-treat Evaluation Group, and 83 failed to return diaries.

2.3 Patient Demographics and Baseline Characteristics

Mean age was 28.3 year (age range from years).
90% of the subjects were Caucasian; 7.1 % were black; 1.8 % were Asian and 0.7 % were other.
Mean BMI (Body Mass Index) was 23.5 kg/m2.
62% of the subjects were nulliparous (has not given live birth).
86% smoked three or fewer cigarettes per day
87% consumed no daily alcoholic beverages
Mean coital frequency was about 9.2 acts per month.

There was no significant difference between starters and switchers in demographic or other baseline characteristics.

2.4 Sponsor's efficacy results

Contraceptive effectiveness was based on the occurrence of pregnancy in the intent-to-treat evaluation group. There were 45 pregnancies reported: 9 pretreatment pregnancies (those in which conception occurred prior to intake of study drug (Vol 1.39, Table 16)); 11 in-treatment pregnancies (those in which conception occurred after the first tablet was taken and prior to discontinuation of the study drug (Vol 1.39 Table 18)); 25 post-treatment pregnancies (those in which conception occurred after discontinuation of the study drug (Vol 1.39 Table 17)). Pregnancy risk was measured by the Pearl Index (Higgins and Wilkens, 1985) and by life-table methods (Cutler and Ederer, 1958).

The Pearl Index is defined as the number of in-treatment pregnancies times 1300 divided by the total number of cycles of exposure. Eleven of the 1226 subjects became pregnant during the drug administration period with a total exposure of 14,049.9 cycles. The Pearl Index for total pregnancies was 1.02 per 100 woman-years. The sponsor also performed a calculation of the Pearl Index which excluded all cycles in which a barrier contraception method was used, the Pearl Index was calculated as 1.11 pregnancies per 100 woman-year.

The Life Table Method estimates the proportion of pregnancies in a fixed time period among a group of subjects who were not pregnant at the start of the period but were at risk of becoming pregnant. The sponsor used the Life Table estimate for the subject in-treatment pregnancies at Cycle 13 (through 364 days). Only 9 pregnancies were included in the Life Table estimation analysis. (One pregnancy occurred in cycle 14 and another pregnancy occurred in cycle 15.) The cumulative life-table estimate was 0.0111. (Vol 1.39, Table 19)

2.5 Reviewer's analyses

This review was based on 11 of the 1,226 subjects becoming pregnant during the drug administration period; the total exposure was 14,049.93 cycles. Thus, the Pearl Index for total pregnancies is 1.0178 per 100 woman-years. This is consistent with the index value of 1.02 reported by the sponsor.

This reviewer used the Lifetest Procedure from SAS to estimate the proportion of pregnancies in a fixed time period among a group of subjects who were not pregnant at the start of the period but were at risk of becoming pregnant.

The only data set provided by the sponsor for an efficacy analysis was STAT2EFF.SD2 on November 28, 1997, which only included 37 of the 45 pregnancies. Data were missing for 7 pre-treatment pregnancies and 1 post-treatment pregnancy. The sponsor did not provide a date of conception for one of the other pre-treatment pregnancies. For this reason this reviewer did not analyze pre-treatment pregnancies.

Among the post-treatment pregnancies identified in the study report, one subject was classified as not pregnant in the dataset and was changed to pregnant by this reviewer. For two subjects

, the sponsor provided no date of conception. This reviewer used information provided ɔm Table 17 of Vol 1.39 and used the number of days after last day of tablet intake information to .ɔcode the date of conception.

Referring to the last row in Table 1, the cumulative failure rate is 0.0109; the 95% confidence interval (CI) is (0.0037, 0.018). This cumulative failure rate compares quite favorably with that reported by sponsor, 0.0111.

Table 1
Pregnancy event rate
Pregnancies conceived while on study drug *

Cycle	Number of subjects entering	Number of pregnancies	Cumulative Pregnancy rate	SE of cumulative pregnancy rate	Lower 95% confidence limit of cumulative pregnancy rate	Upper 95% confidence limit of cumulative pregnancy rate
1	1142	1	0.000875	0.00875	0.000000	0.018025
2	1106	1	0.001780	0.00126	0.000000	0.004250
3	1040	0	0.001780	0.00126	0.000000	0.004250
4	981	0	0.001780	0.00126	0.000000	0.004250
5	951	0	0.001780	0.00126	0.000000	0.004250
6	906	1	0.002880	0.00167	0.000000	0.006153
7	843	1	0.004060	0.00204	0.000062	0.008085
8	814	1	0.005280	0.00238	0.000615	0.009954
9	780	0	0.005280	0.00238	0.000615	0.009945
10	749	2	0.007930	0.00302	0.002011	0.013849
11	739	0	0.007930	0.00302	0.002011	0.013849
12	718	0	0.007930	0.00302	0.002011	0.013849
13	667	2	0.010900	0.00367	0.003707	0.018039

* one of the subjects in the intent-to-treat evaluation group was excluded because conception took place before the first tablet taken; two in-treatment pregnancies occurred after cycle 13 and, therefore, are not included in this table.

A separate Life Table was computed taking into account an additional 3 pregnancies (subjects who were diagnosed as pregnancies conceived after discontinuation of study drug, but less than 28 days after the last tablet taken during the first 13 cycles of the study. The Pearl Index for these 14 pregnancies was 1.295 per 100 woman-years. Referring to the last row in Table 2, the cumulative failure rate is 0.0141, 95% CI is (0.00608, 0.0221).

Table 2
Pregnancy event rate
Pregnancies conceived while on study drug and
Pregnancies conceived after discontinuation of study drug less than 28 days

Cycle	Number of subjects entering	Number of pregnancies	Cumulative Pregnancy rate	SE of cumulative pregnancy rate	Lower 95% confidence limit of cumulative pregnancy rate	Upper 95% confidence limit of cumulative pregnancy rate
1	1142*	1	0.000875	0.000875	0.000000	0.002590
2	1129	1	0.00176	0.00124	0.000000	0.004190
3	1097	0	0.00176	0.00124	0.000000	0.004190
4	1029	0	0.00176	0.00124	0.000000	0.004190
5	969	0	0.00176	0.00124	0.000000	0.004190
6	946	2	0.00387	0.00194	0.000000	0.007672
7	874	1	0.00500	0.00224	0.0006096	0.009390
8	831	2	0.00739	0.00280	0.0019020	0.012878
9	807	0	0.00739	0.00280	0.0019020	0.012878
10	768	3	0.01130	0.00357	0.0043028	0.018297
11	743	0	0.01130	0.00357	0.0043028	0.018297
12	735	0	0.01130	0.00357	0.0043028	0.018297
13	689	2	0.01410	0.00409	0.0060836	0.022116

..6. Review's comments and conclusions

The sponsor concluded that CTR 25 is efficacious for its intended use; and CTR 25 is well-tolerated and is acceptable to women who have previously used OCs, as well as to women who did not previously use oral contraceptives. However, including subjects who were diagnosed as pregnancies conceived after discontinuation of study drug, but less than 28 days after the last tablet taken during the first 13 cycles of the study, increases the Pearl Index from 1.0178 to 1.295 per 100 woman-years. Life Table estimate is also increased from 0.0109, [95% CI: (0.0037, 0.018)] to 0.0141, [95% CI: (0.00608, 0.0221)].

/S/

Moh-Jee Ng, M.S.
Operational Research Analyst

Concur: Dr. Nevius 3/18/98

Dr. Kammerman 3/6/98

cc: Original NDA 20-713
HFD-580/ Division file
HFD-580/ Christine Mauck, M.D., M.P.H.
HFD-580/ Christina Kish
HFD-580/ Lisa Rarick, M.D.

HFD-715/Biometrics Division File,ENevius,LKammerman,MNg,Chron

HFD-580/Amitra,Kraheja

HFD-870/ADorantes,Gbarnette

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This review consists of 6 pages