CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-713

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

KSA

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

NDA:	20-713
Drug:	CTR-25 (Desogestrel and Ethinyl Estradiol) Tablets
Sponsor:	Organon, Inc.
Dates of Submission:	04/30/97 11/26/97
Type of Submission:	Original NDA
Reviewer:	Venkat Jarugula, Ph.D

1. SYNOPSIS

NDA 20-713 for CTR-25 (desogestrel and ethinyl estradiol, USP) tablets was submitted by Organon, Inc. on 04/30/97. The proposed therapeutic indication for this product is oral contraception. CTR-25 dosing regimen consists of 21 days of a 150 μg desogestrel (DSG)/ 20 μg ethinyl estradiol (EE); 2 days of a lactose/starch tablet (placebo); and 5 days of a 10 μg EE tablet. Currently Organon has the following approved DSG containing oral contraceptives (OC) in the market:

Desogen® (USA): 21 days of 150 μg DSG/ 30 μg EE
Marvelon® (Europe): 21 days of 150 μg DSG/ 30 μg EE
Mercilon® (Europe): 21 days of 150 μg DSG/ 20 μg EE and 7 days of placebo

The initial 21-day dosing of CTR-25 is the same as the monophasic regimen for Mercilon® which is approved in over 46 countries world-wide. According to the sponsor, adding five days of 10 μg of EE alone to a 21-day period of fixed combination of DSG and EE in the CTR-25 regimen reduces the total estrogen dose per cycle compared with 30-35 μg EE containing OCs.

To support the approval of CTR-25, the following three pharmacokinetic studies were submitted in the Human Pharmacokinetics and Bioavailability section of the NDA:

1. Study 086001: "An Open Label Multicenter Non-Comparative Safety and Efficacy Study of Desogestrel Containing Oral Contraceptive, CTR-25 (Pharmacokinetic Subset G)".

2. Study 086002: "A Single Dose Study of the Bioavailability of CTR-25 (150 μg DSG/20 μg EE Tablet) Relative to a Combination Solution".

3. Study 086003: "A Single Dose Study of the Bioavailability of CTR-25 (10 μg EE Tablet) relative to an EE solution".

The overall results obtained in these pharmacokinetic studies have shown that:

1. Following oral administration of CTR-25, DSG is rapidly absorbed and metabolized to etonogestrel (ENG), which is the biologically active form. Since DSG could not be detected in plasma, the pharmacokinetics of CTR-25 were evaluated by measuring the serum concentrations of ENG and EE.

2. The mean relative bioavailability of ENG based on $AUC_{0-\infty}$ from CTR-25 tablets vs solution was 100%.

3. The mean relative bioavailability of EE based on $AUC_{0-\infty}$ was 93% and 97% from 150 μg ENG/20 μg EE and 10 μg EE tablet, respectively, when compared to their respective reference oral solutions.

4. Following multiple dose administration of CTR-25, the steady-state plasma concentrations of ENG and EE were reached within Day 21.

5. The accumulation of ENG upon multiple dose administration was 2.2 times. This values is slightly more than expected from its elimination half-life. The accumulation of EE (1.05) was underestimated due to the contribution of residual plasma levels carried over from the administration of 10 μg EE tablets in the second cycle.

6. The pharmacokinetics of EE upon multiple dosing is dose proportional between the 10 μg and 20 μg doses.

2. RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II) has reviewed the Human Pharmacokinetics and Bioavailability section of the NDA 20-713 submitted on 04/30/97 and recommends the following:

1. The pharmacokinetics and bioavailability of CTR-25 tablets have been adequately characterized. Therefore the information proposed in the NDA satisfactorily meets the requirements of OCPB and is acceptable.

2. The proposed dissolution method and the specifications are acceptable.

3. The sponsor's request for a waiver of the requirement for the submission of *in vivo* bioequivalence data for the commercial and clinical trial formulations of CTR-25 tablets can be granted based on the *in vitro* comparative dissolution data.

4. The proposed labeling should be modified as recommended in the Labeling section of this review (pages 15-17) and resubmitted for review.

5. Sponsor should provide information regarding the specific enzymes responsible for the metabolism of desogestrel for review. If the information is not available, the sponsor should conduct an

Please convey the Recommendation and the labeling comments to the sponsor as appropriate.

/S/ 3/12/98

Venkateswar R. Jarugula, Ph.D.

RD initialed by Angelica Dorantes, Ph.D. AD 2/20/98

FT initialed by Angelica Dorantes, Ph.D. 3/12/98

cc: NDA 20-713, HFD-580 (Rarick, Kish), HFD-870 (M.Chen, Donates, Jarugula), CDR (B.Murphy for Drug)

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3. BACKGROUND

For the past several decades, oral contraceptives have been one of the common birth control methods used by women. Although combination oral contraceptives (OCs) are generally very safe, they are not totally free of adverse effects. Optimizing the estrogen dose has always been a goal in the development of combination OCs. The estrogen component of the earlier OCs was initially up to 150 μg per tablet and it has been greatly reduced over the years in response to laboratory and epidemiological findings of the association between the estrogen dose and the risk of vascular complications. In combination with the older progestins, 30 to 40 μg EE was found to be lowest estrogen dose with good efficacy and cycle control.

Organon is developing CTR-25 as OC tablets with the objective of reducing the estrogen dose in combination with desogestrel, a new generation of selective progestins, originally synthesized by Organon. The CTR-25 regimen (28 days) consists of : 21 days of a 150 μg DSG/20 μg EE tablet; 2 days of a lactose/starch tablet (placebo); and 5 days of 10 μg EE tablet. According to the sponsor, adding five days of 10 μg EE alone in the CTR-25 regimen serves the following purposes:

- Reduce the total estrogen dose per cycle compared with 30-35 μg EE-containing OCs,
- Stimulate endometrial progestin receptors, which may improve cycle control,

- Reduce escape ovulations when a dosage unit is missed, because of reduced pill free interval.

4. FORMULATION

The quantitative composition of the tablets used in dosage regimen for CTR-25 for IND studies as well as to be marketed formulations is summarized in Table 1.

Table 1. Composition of CTR-25 tablets used in IND studies and the to-be marketed formulation

Formulation No:	PD0335A	PD0335C	PD0335B
Study No:	086001 086002	086001 086003	086001
Ingredients			
Core Composition (mg/tablet)			
✓Desogestrel	0.15	NP	NP
✓Ethinyl Estradiol, USP			
✓Vitamin E, USP			
✓Corn Starch, NF			
✓Povidone, USP			
✓Stearic Acid, NF			
✓Colloidal Silicone Dioxide, NF			
✓Lactose, Hydrous, NF q.s. to			
✓Magnesium Stearate, NF			
Coating Solution (mg/tablet)			
✓Hydroxypropyl Methylcellulose 2910, USP			
✓Polyethylene Glycol 400, NF			
✓Titanium Dioxide, USP			
✓Ferric Oxide, Yellow, NF			
✓FD&C Blue No.2 Al Lake			
✓Talc, USP			

a removed during processing

b removed during processing. Only used in the clinical batch (PD0335) and will not be used in the market formulations.

NP Not present

5. *IN VITRO* DISSOLUTION

The sponsor proposed the following dissolution method and specifications:

Apparatus	USP Dissolution II Paddle Vankel 7000 (or equivalent)
Medium	0.05% Sodium lauryl sulfate in purified water
Volume	500 ml
Temperature	$37^0C \pm 0.5^0C$
Paddle Speed	50 rpm
Specification for DSG	Q= % in minutes
Specification for EE	Q= % in minutes

Reviewer Comment:

1. The proposed dissolution method and the specifications are reasonable for an immediate release tablet dosage form and are similar to those approved for Desogen®. Therefore, the proposed dissolution method and specifications are acceptable.

6. BIO-WAIVER REQUEST

As shown in Table 1, the formulations of the DSG/EE combination, placebo and EE tablets used in the IND clinical studies are identical to the proposed market formulations except for the following variations:

As agreed by the Division of Biopharmaceutics of the FDA , the sponsor is requesting a waiver of bioequivalence data for these minor modifications. Comparative dissolution data (presented in Table 2 and 3) were submitted to support the bio-waiver request and the similarity factors (f_2) are listed Table 4.

Table 2. Comparative dissolution data for the 150 μg DSG/20 μg EE tablets as % dissolved (average of 12 tablets)

	15 minutes		30 minutes		45 minutes		60 minutes	
Batch number	DSG	EE	DSG	EE	DSG	EE	DSG	EE
PD0335 (CP03113) Clinical Batch	83.7	84.1	89.4	91.7	90.3	92.6	89.4	92.3
060181/ 049891001 The Netherlands	85.6	90.5	90.6	96.0	91.9	97.5	93.7	98.2
060182/ 046129001 The Netherlands	89.8	90.2	94.6	95.7	96.0	96.5	98.3	97.3

Method: USP Dissolution Apparatus 2 (Paddle method), 50 RPM, 0.05% SLS in water, 500 ml.

Table 3. Comparative dissolution data for the 10 μg EE tablets as % dissolved (average of 12 tablets)

Batch Number	15 minutes	30 minutes	45 minutes	60 minutes
PD0335 (CP093114) Clinical Batch	86.1	95.0	96.4	97.0
060181/ 046131001 The Netherlands	92.1	94.8	95.0	96.9
060182/ 05631001 The Netherlands	91.6	93.3	94.4	95.5

Table 4. Similarity factors (f_2) for the comparative dissolution data

Clinical Batch	Stability Batch	f_2	f_2
		DSG	EE
150 mg DSG/ 20 mg EE tablets			
PD0335 (CP093113)	060181/04989100	78.1	81.3
PD0335 (CP093113)	060182/046129001	58.7	80.7
10 mg EE tablets			
PD0335 (CP093114)	060181/046131001	----	74.9
PD0335 (CP093114)	060182/056310001	----	75.2

Reviewer's Comments:

1. The calculated f_2 values for the dissolution comparison between the clinical batches and the to be marketed batches are greater than 50. Therefore, according to SUPAC guidance for immediate release tablets, the *in vitro* dissolution of the to be marketed formulation is similar to the clinical trials formulation.

2. Based on the comparative dissolution data, the sponsor's bio-waiver request is acceptable.

7. ANALYTICAL METHODOLOGY

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Reviewer's Comment:

Overall, the assay validation parameters for both analytical centers are within acceptable limits and the assay methods used for the measurement of ENG and EE are found to be acceptable.

8. PHARMACOKINETICS

The pharmacokinetic studies provided to support the approval of CTR-25 are summarized in Table 8.

Table 8. Summary of pharmacokinetic studies:

Study No:	Objective	Dosing	No. of subjects
086002	Relative Bioavailability in comparison to a reference solution	CTR-25 tablets Single dose of two tablets each containing 150µg DSG/20µg EE Ref. Solution Single dose of two 5 ml aliquots each containing 150µg DSG/20µg EE	20
086003	Relative Bioavailability in comparison to a reference solution	CTR-25 tablets Single dose of Two tablets each containing 10µg EE Ref. Solution Single dose of Two 5 ml aliquots each containing 10µg EE	20
086001	Safety and efficacy of CTR-25 regimen (Steady-state PK)	CTR-25 tablets 150µg DSG/20µg EE (Days 1-21) Placebo (days 22-23) 10µg EE (days 24-28)	24

A. BIOAVAILABILITY

Two studies were conducted to assess the relative bioavailability of CTR-25 tablets. Study 086002 determined the bioavailability of 150 µg DSG/20 µg EE combination tablet compared to a combination solution while study 086003 compared the bioavailability of 10 µg EE tablet with an EE oral solution.

The pharmacokinetic parameters and relative bioavailability of ENG and EE are summarized in Table 9 and the mean plasma levels of ENG and EE are illustrated in Figure 1 and 2, respectively.

Table 9. Pharmacokinetic parameters of ENG and EE

	C_{max} (pg/ml)	T_{max} (hr)	$T_{1/2}$ (hr)	$AUC_{(0-\infty)}$ (pg/ml-hr)	F*
ENG					
Tablets (Test) Arithmetic Mean Geometric LS Mean	 3234.71 3076.86	 1.47	 38.35 33.84	 29290.08 27686.63	1.00
Solution (Reference) Arithmetic Mean Geometric LS Mean	 2771.76 2656.73	 1.16 ND	 37.82 35.03	 29623.69 27686.63	
EE from combination					
Tablets (Test) Arithmetic Mean Geometric LS Mean	 110.46 107.21	 1.67 ND	 21.82 21.11	 1069.37 1002.43	0.93
Solution (Reference) Arithmetic Mean Geometric LS Mean	 122.43 119.39	 0.80 ND	 20.89 20.66	 1164.13 1077.04	
EE alone					
Tablets (Test) Arithmetic Mean Geometric LS Mean	 61.48 57.77	 1.48 ND	 35.69 32.72	 680.62 663.29	0.99
Solution (Reference) Arithmetic Mean Geometric LS Mean	 74.74 71.99	 0.96 ND	 33.42 31.73	 688.34 673.75	

*F = Geometric mean ratio of $AUC_{(0-\infty)}$

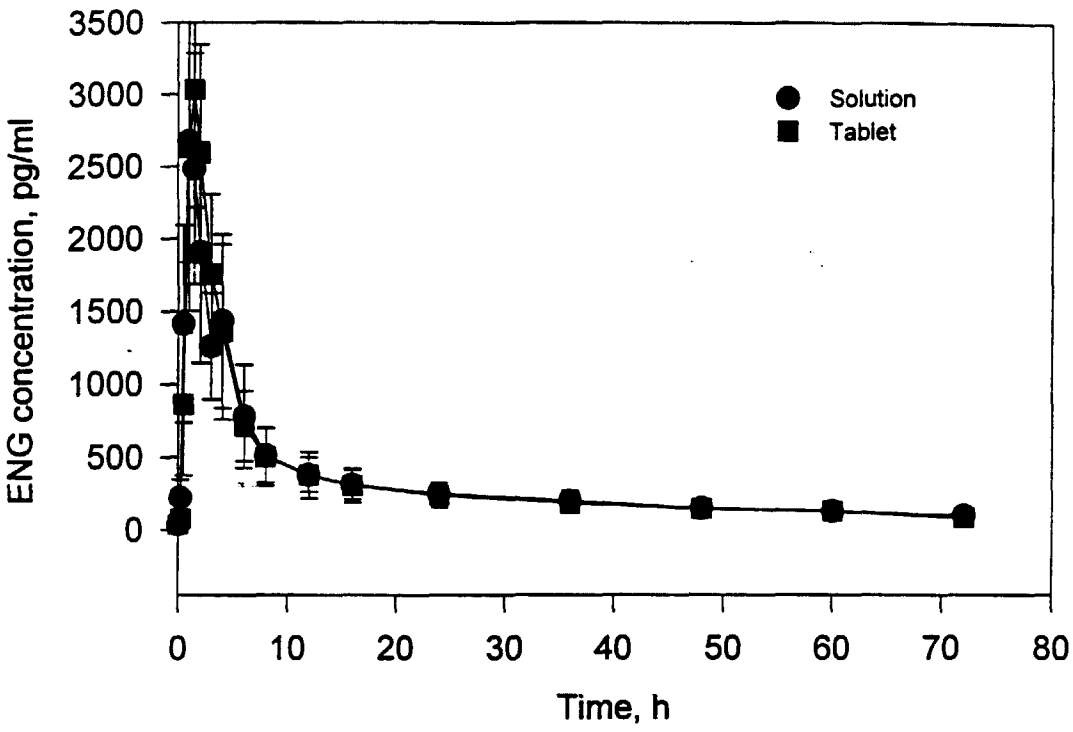

Fig.1 Mean plasma concentration of ENG following single dose administration of tablet and solution in Study 086002

Bioavailability of ENG:

The mean relative bioavailability of ENG as estimated from $AUC_{0-\infty}$ was 100% with confidence limits of 88% to 114%. The mean C_{max} of ENG of the tablet was 116% of that from the reference solution with confidence limits of 98% to 137%. The time to reach peak concentration T_{max}, as expected was significantly longer for the tablets (1.47 hr) than for the solution (1.16 hr). There was no significant difference in elimination half-lives between the tablet and solution (p=0.77).

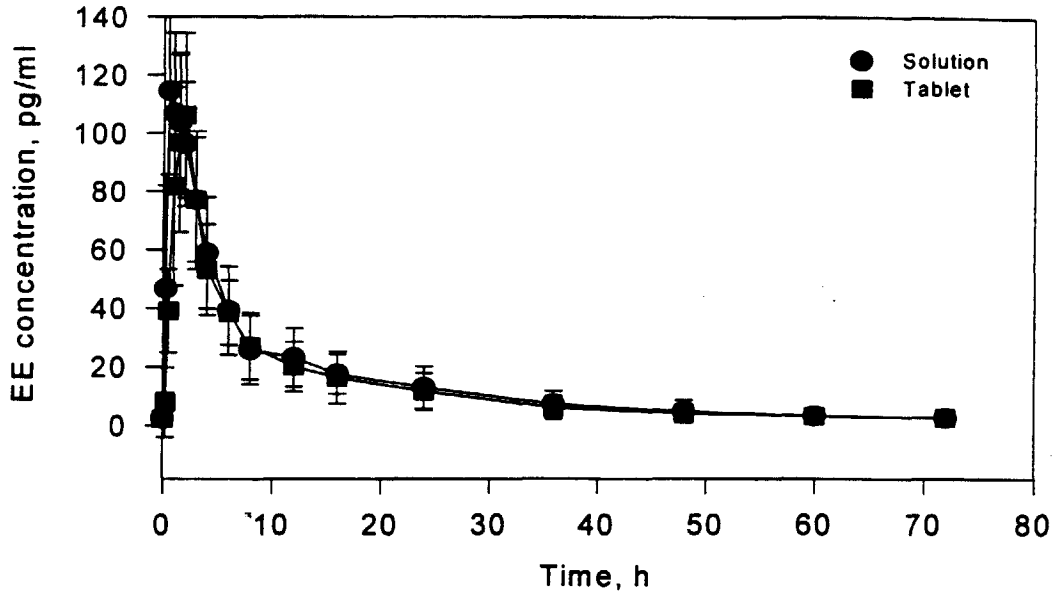

Fig. 2 Mean plasma concentrations of EE following the administration of tablet and solution in Study86002.

Bioavailability of EE from combination tablet:

The mean relative bioavailability of EE based on $AUC_{0-\infty}$ was estimated to be 93%, with confidence limits of 87% to 99%. The mean C_{max} of EE from the tablet was 90% relative to that of the reference solution while the mean T_{max} for the tablet was 1.67 hrs compared to 0.8 hrs for the solution. There was no significant difference in the elimination half-lives between the tablet and the solution (p=0.49).

Bioavailability of EE from 10 μg EE tablet:

The estimated mean relative bioavailability of EE from the 10 μg tablet was 99% with confidence limits of 90% to 104%. As expected, the mean C_{max} of EE from the tablets was 80% of that from the solution and the T_{max} was longer for the tablet (1.48 hrs) than for the solution (0.96). The elimination half-lives of EE from the tablet and the solution were comparable.

Reviewer's Comments:

1. The administration of the 150 μg DSG/20μ EE tablets resulted in high bioavailability for both ENG(100%) and EE (93%) when compared to that from a combination solution containing equal amounts of DSG and EE.

2. Although the rate of absorption, as evidenced by C_{max}, of ENG from tablet was unusually higher than that from the solution, the difference was not statistically significant.

3. The overall results of these studies show that both ENG and EE are rapidly absorbed from the tablet formulation following oral administration.

B. Multiple dose/Steady state PK:

The steady state pharmacokinetics of CTR-25 tablets was investigated in a subset of patients in phase III clinical study 086001. This was an open-label, multicenter safety and efficacy study in 1250 subjects. The pharmacokinetic analysis was performed on a subset of 24 subjects from a single center. Seventeen of these subjects had complete data for pharmacokinetic analysis. The pharmacokinetic parameters of ENG and EE following multiple dose administration of CTR-25 regimen for three cycles are summarized in Table 10 and the mean serum concentration profiles of ENG and EE are illustrated in Figures 3 and 4, respectively.

Table 10. Multiple dose pharmacokinetic parameters of ENG and EE

Compound	Day	$AUC_{(0-24)}$ (pg.hr/ml)	$AUC_{(0-\infty)}$ (pg.hr/ml)	C_{max} (pg/ml)	T_{max} (hr)	$t_{1/2}$ (hr)
ENG	1	17832 (5674)	35993 (16929)	2504 (988)	2.44 (1.0)	29.8 (16.3)
	21	39391 (12134)	79878 (29120)	4091(1186)	1.59 (0.71)	27.8 (7.2)
EE	1	566 (173)	867 (301)	51.9 (15.4)	2.91 (1.24)	16.5 (4.8)
	21	597 (127)	1094 (675)	62.2 (25.9)	2.00 (0.82)	23.9 (25.5)
	24	246 (65)	391 (114)	24.6 (10.8)	2.38 (1.05)	18.7 (10.3)
	28	312 (62)	481 (103)	35.3 (27.5)	2.09 (1.35)	18.9 (8.3)

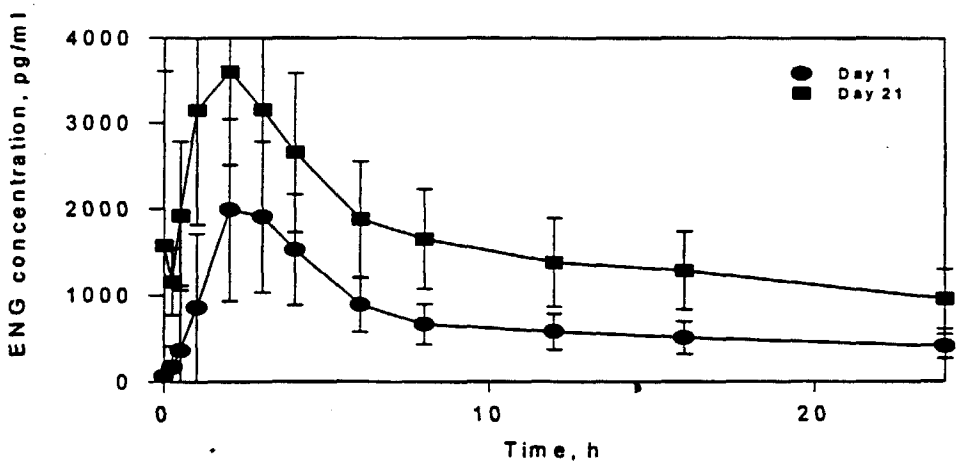

Fig.3 Mean plasma concentrations of ENG following multiple dose administration of CTR-25 tablets (Study 086001).

There was an increase of 9% in AUC_{0-24} and 63% in C_{max} of ENG on Day 21 of third cycle when compared to $AUC_{0-\infty}$ and C_{max} on Day 1 in third cycle. However there was no change in half-life of ENG from Day 1 to Day 21 upon multiple administration.

For EE, AUC_{0-24} decreased by 31% and C_{max} increased by 20% on Day 21 of third cycle when compared to $AUC_{0-\infty}$ and C_{max} on Day 1 of third cycle. The terminal half-life values remain

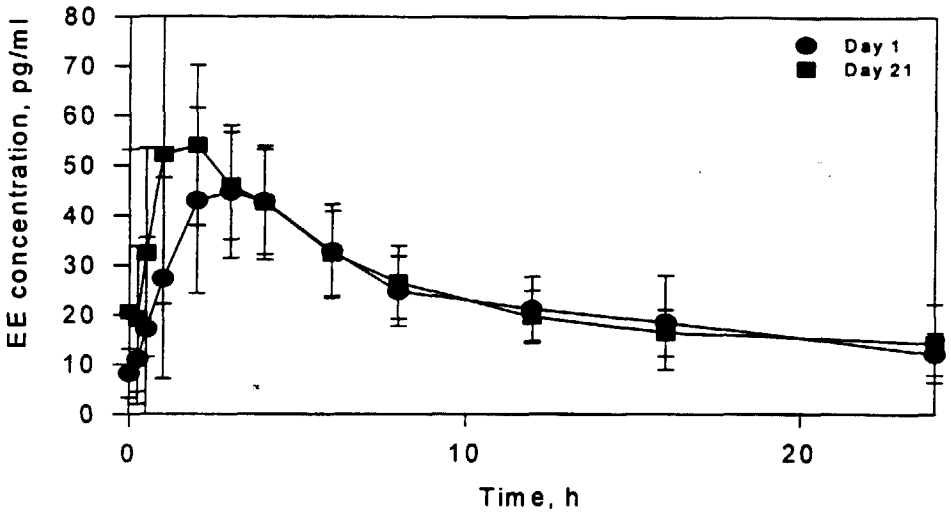

Fig.4 Mean plasma concentrations of EE following multiple dose administration of CTR-25 tablets (Study 086001).

unchanged from Day 1 to Day 21. The decrease in AUC and mere 20% increase in C_{max} may be due to the fact that the Day 1 AUC and C_{max} are overestimated because of residual EE concentrations accumulated from the administration of EE 10 μg tablets on Day 24 – 28 in second cycle.

The accumulation factors for ENG and EE upon multiple dose administration were computed from C_{min}, C_{max} and AUC_{0-24} values on Day 1 and Day 24 by this reviewer and are summarized in Table 11.

Table 11. Accumulation factors of serum ENG and EE at steady-state

Parameter	Day 1	Day 21	Acc.factor
ENG			
C_{min}	408.2	956.1	2.34
C_{max}	2503.59	4091.18	1.63
AUC_{0-24}	17832.53	39391.35	2.21
EE			
C_{min}	12.1	14.3	1.18
C_{max}	51.88	62.23	1.19
AUC_{0-24}	565.76	596.98	1.05

Reviewer Comments:

1. It should be noted that plasma concentrations of ENG and EE were not measured on Day 1 of Cycle 1. Therefore pharmacokinetic parameters obtained on Day 21 of Cycle 3 were compared to those on Day 1 of Cycle 3. As a result of this, the pharmacokinetic parameters AUC, C_{max} of both compounds on Day 1 of Cycle 3 might be over estimated. This is more so in the case of EE because of previous dosing of 10 μg tablets from Day 24 – 28 on Cycle 2. However the contribution of residual concentrations of ENG on Day 1 of Cycle 3 may not be significant because of preceding 7-day DSG free period.

2. The plasma concentrations of ENG and EE have been shown to reach steady-state prior to Day 21 of Cycle 3 upon multiple administration of CTR-25 regimen.

3. As expected with the multiple dose administration of EE, the mean serum SHBG levels on Day 1 of Cycle 3 (115.7 nmol/L) were above the normal limit of 30 -95 nmol/L and were further increased by 14% to 132.1 nmol/L on Day 21 of Cycle 3. However, median free and total testosterone concentrations remained fairly constant throughout the third cycle and were within normal range.

4. The accumulation of ENG appears to be slightly more than that expected from its elimination half-life. This could be due to the increase in serum SHBG levels caused by the multiple dosing of EE. The accumulation of EE was under estimated because of residual plasma levels of EE accumulated from Cycle 2.

C. Dose Proportionality for EE:

The dose proportionality of EE was evaluated in study 086001 (see Table 10). The results of this study showed that when the dose of EE was decreased from 20 μg on Day 1 through 21 to 10 μg on Day 24 through 28, $AUC_{(0-24)}$ decreased by 48% from 597 pg.hr/ml on Day 21 to 312 pg.hr/ml on Day 28. Similarly, C_{max} decreased by 43% from 62.2 pg/ml on Day 21 to 35.3 pg/ml on Day 28 indicating the dose proportionality for EE.

Reviewer Comment:

The results of study 86001 demonstrated that the pharmacokinetics of EE were dose proportional between 10 and 20 μg.

8. LABELING

The proposed labeling should be rewritten as shown below:

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APPENDIX I

(Summary of Individual Study Reports)

9.1 Summary of Individual Study Reports:

9.1.1 Study 086002

Title: "A Single Dose Study of the Bioavailability of CTR-25 (150 μg DS/20 μg EE Tablet) Relative To A Combination Solution".

Objective: To determine the bioavailability of 3-k-DSG and EE from a 150 μg DSG/20 μg EE tablet relative to a solution containing the same amount of active ingredients.

Investigator:
Study Site:

Study Design: Open label, randomized, single dose, 2-way crossover study

No. of Subjects: Twenty healthy female subjects in the age range of 18-30 years were enrolled. Eighteen (18) subjects completed the study and two (2) were discontinued.

Dosage administration: Subjects received the following treatments of single dose according to randomization schedule in two consecutive cycles on day 2,3,4,5,6,or 7:

CTR-25 tablets:	DSG/EE (150 μg/20 μg) (Batch Number PD0335A)	Single oral dose of two tablets
Solution:	DSG/EE (150 μg/20 μg) (Batch Number PD0383)	Single oral dose of two aliquots

Table 1. Composition of Reference solution

Formulation No. Study used in:	PD0383 086002	PD0384 086003
Ingredients	150 μg DSG/ 20 μg EE solution	10 μg EE solution
Composition (amount/5 ml)		
Desogestrel	mg	NP
Ethinyl Estradiol, USP	mg	mg
Ethyl Alcohol, USP	ml	ml
Glycerin, USP	mg	mg
	ml	ml

Sample Analysis:
Venous blood samples (15 ml) were collected at -24, 0, 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60 and 72 hrs after dose administration. Serum samples were assayed for ENG and EE by Serum sexual

hormone binding globulin (SHBG) were measured from blood samples taken at 0 hr of Cycle 1 and 2.

Assay Performance Summary During Sample Analysis

	ENG	EE
Calibration Range:	pg/ml	pg/ml
Calibration Standards:		
Average correlation coefficient:	0.9995	0.9997
Coefficient of Variation:	3.23% to 9.92%	2.88% to 6.86%
% Difference from Theoretical con.	-3.74% to 2.92%	-0.38% to 0.43%
Quality Control Standards:		
Coefficient of Variation	5.54% to 10.5%	7.52% to 14.3%
%Difference from Theoretical	-7.42% to -1.85%	-3.55% to -3.2%

For assay validation details, please see the Analytical Methodology section of the review.

Results:

Table 2. Pharmacokinetic parameters of ENG

	C_{max} (pg/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	$AUC_{(0-72)}$ (pg/ml-hr)	$AUC_{(0-\infty)}$ (pg/ml-hr)
Tablets (Test)					
Arithmetic Mean	3234.71	1.47	38.35	23545.05	29290.08
Geometric LS Mean	3076.86		33.84	22619.77	27686.63
Solution (Reference)					
Arithmetic Mean	2771.76	1.16	37.82	23152.08	29623.69
Geometric LS Mean	2656.73	ND	35.03	22273.47	27686.63
Point Estimate	1.16	0.25	0.97	1.02	1.00
95% Confidence Limits	0.98 - 1.37	0.25-0.44	0.75-1.24	0.97-1.07	0.88-1.14
Significant Difference ($p \leq 0.05$)	No	Yes	No	No	No

Table 3.Pharmacokinetic Parameters for EE

	C_{max} (pg/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	$AUC_{(0-72)}$ (pg/ml-hr)	$AUC_{(0-\infty)}$ (pg/ml-hr)
Tablets (Test) Arithmetic Mean Geometric LS Mean	 110.46 107.21	 1.67 ND	 21.82 21.11	 981.77 923.95	 1069.37 1002.43
Solution (Reference) Arithmetic Mean Geometric LS Mean	 122.43 119.39	 0.80 ND	 20.89 20.66	 1088.20 10.32.14	 1164.13 1077.04
Point Estimate 95% Confidence Limits	0.90 0.77-1.05	0.98 0.51-1.14	1.02 0.96-1.09	0.90 0.81-0.99	0.93 0.87-0.99
Significant Difference ($p \leq 0.05$)	No	Yes	No	Yes	Yes

Sponsor's Conclusions:

ENG:

1. The estimated mean relative bioavailability of (F) of DSG (measured as ENG was 100% and the truncated mean relative BA was 102%.
2. Although the (geometric) mean peak serum concentration of ENG was higher from the tablets as compared to the solution, the difference was not statistically significant.
3. The T_{max} was lower for tablets when compared to the solution which is expected .
4. The elimination half-life was similar for both tablet and solution indicating the clearance of the drug is same for the tablets as well as solution.

EE

1. The estimated mean relative bioavailability of EE from tablets was 93% relative to the solution.
2. There was no significant difference in the mean C_{max} of EE from the tablet and solution formulations while the T_{max} from tablets was significantly lower.

Serum SHBG:

1. Serum SHBG concentrations increased slightly following both the tablet and solution administrations, but the increase was not considered clinically significant.

Reviewer's Comment

The study proved that the active ingredients ENG and EE were rapidly absorbed with high relative bioavailability from the tablet formulation when compared to solution and the sponsor's conclusions are appropriate.

9.1.2 STUDY 086003

Title: "A Single Dose Study of the Bioavailability of CTR-25 (10 μg EE Tablet) Relative to EE (10 μg) Solution".

Objective: To determine the oral bioavailability of EE in a 10 μg EE CTR-25 tablet relative to a solution containing 10 μg EE".

Investigator:
Study Site:

Study Design: Open label, randomized, single dose crossover study

No. of Subjects: Twenty (20) healthy female subjects between ages 18-30 years were enrolled and eighteen (18) completed the study.

Dosage and Administration:
Subjects were randomly assigned to receive the following treatments of single dose in two consecutive cycles:

CTR-25 tablets (Test): EE (10 μg) Single oral dose of two tablets (20 μg)
Batch No. PD0335C

Solution (reference): EE (10 μg in 5 ml) Single oral dose of 10 ml (20 μg)
Batch No. PD0384

Sample Collection:
Venous blood samples were collected at -24, 0, 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60 and 72 hrs following the drug administration and serum concentrations of EE were measured by

Assay Performance: Done at For details regarding assay performance during sample analysis, please refer to Individual Summary of Study 86002.

Results:

Table 4. Pharmacokinetic Parameters of EE:

	C_{max} (pg/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	$AUC_{(0-72)}$ (pg/ml-hr)	$AUC_{(0-\infty)}$ (pg/ml-hr)
Tablets (Test)					
Arithmetic Mean	61.48	1.48	35.69	588.65	680.62
Geometric LS Mean	57.77	ND	32.72	563.07	663.29
Solution (Reference)					
Arithmetic Mean	74.74	0.96	33.42	603.47	688.34
Geometric LS Mean	71.99	ND	31.73	581.87	673.75
Point Estimate	0.80	0.56	1.03	0.97	0.99
95% Confidence Limits	0.68-0.94	0.24-0.75	0.87-1.22	0.90-1.04	0.93-1.04

Sponsor's Conclusions

1. The estimated mean relative bioavailability of EE compared to a solution was 99% and mean truncated relative bioavailability was 97%.
2. As expected, the mean C_{max} was lower and T_{max} was higher for the tablet.

Reviewer's Comments

1. The bioavailability of EE from the tablet formulation was essentially equal to that from oral solution and the absorption is rapid from both formulations although from the tablets it is relatively slower.
2. The absorption characteristics of EE from this study and from the Study 086002 are comparable indicating that the presence of DSG in the formulation did not effect the single dose pharmacokinetics of EE.

9.1.3 Subset Study 086001

Title: "An Open Label Multicenter Non-Comparative Safety and Efficacy Study of the Desogestrel Containing Oral Contraceptive, CTR-25".

Objective: To evaluate the steady-state pharmacokinetic parameters of CTR- 25 in approximately 18 subjects from the main study population.

Investigator:

Study Site:

Study Design: Open label, non-comparative, single center subset investigation

No. of subjects: Twenty four (24) subjects were enrolled in this subset and 17 had sufficient data for pharmacokinetic analysis.

Dosage and Administration:
Subjects received CTR-25 tablets during each menstrual cycle for 3 cycles as follows:

Days 1-21	DSG 150 µg/EE 20 µg	Batch No. PD0335A
Days 22 & 23	Placebo	Batch No. PD0335B
Days 24-28	EE 10µg	Batch No. PD0335C

Sample collection:
To determine the steady-state pharmacokinetics of ENG and EE, blood samples (9 ml) were collected at -24, 0, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours after drug administration on Days 1, 21, 24, and 28 of the third cycle. Serum concentrations of ENG and EE were analyzed by The details of assay validation can be found in Analytical Methods section of the review.
Blood samples were also collected for SHBG, free testosterone and total testosterone at screening and at 0 hour (immediately prior to drug administration) on days 1, 21, 24, and 28 of cycle 3.
$AUC_{(0-24)}$, $AUC_{(0-\infty)}$, C_{max}, T_{max}, K_{elim} and $t_{1/2}$ were determined from serum concentration versus time data. Attainment of steady-state was evaluated using a univariate ANOVA of the -24, 0, and 24 hour serum concentrations for ENG and EE on day 21.

Assay Performance Summary During the Sample Analysis:

	ENG	EE
Calibration Range	pg/ml	pg/tube
Calibration Standards		
Coefficient of Variation	2.3% to 18.0%	2.7% to 31.9%
% Difference from Theoretical	-3.7% to 6.0%	0.0% to 12.0%

Quality Control Standards

Coefficient of Variation:	8.4% to 15.7%	8.2% to 22.4%
% Difference from Theoretical	-8.5% to -4.2%	-3.3% to 6.2%

Results

The summary of pharmacokinetic parameters for ENG and EE on day 1 and day 21 of the third cycle are summarized in Table 6 and the summary of serum SHBG, free T and total T concentrations is included in Table 7.

Table 6. Mean (SD) pharmacokinetic parameters of ENG and EE upon multiple dosing

Compound	Day	$AUC_{(0-24)}$ (pg.hr/ml)	$AUC_{(0-\infty)}$ (pg.hr/ml)	C_{max} (pg/ml)	T_{max} (hr)	$t_{1/2}$ (hr)
ENG	1	17832 (5674)	35993 (16929)	2504 (988)	2.44 (1.0)	29.8 (16.3)
	21	39391 (12134)	79878 (29120)	4091(1186)	1.59 (0.71)	27.8 (7.2)
EE	1	566 (173)	867 (301)	51.9 (15.4)	2.91 (1.24)	16.5 (4.8)
	21	597 (127)	1094 (675)	62.2 (25.9)	2.00 (0.82)	23.9 (25.5)
	24	246 (65)	391 (114)	24.6 (10.8)	2.38 (1.05)	18.7 (10.3)
	28	312 (62)	481 (103)	35.3 (27.5)	2.09 (1.35)	18.9 (8.3)

Table 7. Summary SHBG, free T and total T concentrations at 0-hour each day

Parameter	Day 1		Day 21		Day 24		Day 28	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
SHBG (nmol/L)	115.7	43.4	132.1	46.0	132	45.9	124.1	44.3
Free T (pg/ml)	0.8	0.2	0.9	0.4	0.8	0.3	1.1	0.7
Total T (ng/dl)	37.2	16.3	36.9	20.7	36.5	20.7	53.6	65.8

Normal Ranges: SHBG 30-95 nmol/L
Free T Up to 3.8 pg/ml
Total T 22-80 ng/dl

Sponsor's Conclusions:

1. Both ENG and EE reached steady-state plasma levels within 21 days of multiple dose administration of CTR-25.

2. The plasma levels of free and total testosterone and SHBG are relatively consistent for the duration of the study.

3. The pharmacokinetics of EE is dose proportional based on the data obtained on Day 21 and Day 28 of Cycle 3.

Reviewer's Comments:

1. It should be noted that the plasma levels of ENG and EE were not measured on Day 1 of the first Cycle. Therefore the plasma levels of both drugs on Day 21 of Cycle 3 were compared to those on Day 1 of Cycle 3. Consequently, the pharmacokinetic parameters on Day 1 of Cycle 3 are overestimated for EE because of residual concentrations resulting from the administration of 10 μg EE tablets from Days 24-28 on Cycle 2. Because of this, the accumulation factor of EE could not be determined accurately. However, it is known from other combination oral contraceptives that EE does not accumulate more than expected form it elimination half-life.

2. As expected with the multiple dose administration of EE, the mean serum SHBG levels on Day 1 of Cycle 3 (115.7 nmol/L) were above the normal limit of 30 -95 nmol/L and were further increased by 14% to 132.1 nmol/L on Day 21 of Cycle 3. However, median free and total testosterone concentrations remained fairly constant throughout the third cycle and were within normal range.

3. The accumulation of ENG (2.2) is slightly more than expected (1.19) from its elimination characteristics may be because of the fact that the production of SHBG is increased by the multiple dose administration of EE.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-713

ADMINISTRATIVE DOCUMENTS

NDA 20-713
CTR 25 (desogestrel and ethinyl estradiol)
Organon Inc.

Group Leaders Memo

The Medical Officer's review of this application was evaluated by the Division Director, acting in the capacity of Group Leader therefore a Group Leaders memo is not necessary.

NDA 20-713
CTR 25 (desogestrel and ethinyl estradiol)
Organon Inc.

Microbiology Review

This application does not require a microbiology review.

NDA 20-713
CTR 25 (desogestrel and ethinyl estradiol)
Organon Inc.

Federal Register Notice

This application has not been the subject of a Federal Register Notice.

NDA 20-713
CTR 25 (desogestrel and ethinyl estradiol)
Organon Inc.

Advertising Material

Advertising material has not been submitted for this application.

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 20 713 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD 575 Trade and generic names/dosage form: Tradename (desogestrel and ethinyl estradiol) Tablets Action: AP AE NA

Applicant Organon Therapeutic Class 3

Indication(s) previously approved None

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Proposed indication in this application Contraception

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) X No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing,

___ (2) Protocols were submitted and approved.

___ (3) Protocols were submitted and are under review.

___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply, attach an explanation, as necessary.**

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes X No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Division Director (e.g., medical review, medical officer, team leader)

Signature of Preparer and Title

3/4/96
Date

Orig NDA/BLA # 20 713
HFD 575/Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

KIS1

NDA 20-713

OCT - 8 1997

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

Dear Mr. Mayo:

Please refer to your pending April 30, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Desogen-20 (desogestrel and ethinyl estradiol) Tablets.

We have completed our review of the Chemistry Manufacturing and Controls section of your submission and have identified the following deficiencies:

1. The tests and methods used for should be provided.

2. The sampling plan used during the manufacturing process for the drug product should be submitted.

3. The specifications for the particle size of the active granules and basic granules should be provided.

4. The batch records for four commercial batches manufactured in Ireland (desogestrel/ethinyl estradiol tablet batch # E5143-00A & E54144-00A; ethinyl estradiol tablet batch # E55550-00A & E55551-00A) should be provided. These four batches were used for *in-vitro* dissolution studies (vol. 1.4, pg. 16).

5. The batch record for placebo tablets #CP093112 should be provided. This batch was used for clinical and stability studies.

6. The sampling plan from the in-process controls are insufficiently detailed to be acceptable. Although fragments of the sampling plan can be found in the master batch record and also the batch records themselves, it should be described in detail in the narrative section of the NDA. In addition, the narrative description does not give the rationale behind the sample size taken. A description of the number of samples taken and locations where the samples are taken should also be provided.

7. Information on what action will be taken when deviations from specifications occur during manufacture should be provided.

8. A description of the sampling plan for production batches and selection of samples for analyses should be provided. The sampling plan is needed to assess whether the finished product tablets are within specified release specifications.

9. A letter of authorization from should be provided.

10. The 12 month stability data from the two most recent batches (#060181 & 060182) does not at this time support the proposed 3 year expiration date. All the data for assay (vol. 1.7, pg. 119-124, with the exception of pg. 124) show that the percent label claim is increasing with time. The assay data (pg. 130) for ethinyl estradiol in the 150 ug desogestrel/20 ug ethinyl estradiol tablet indicate at 3 years the percent label claim will be over the % specification. The reason for the increase in percent label claim does not appear obvious. An interpretation of this currently submitted data should be provided. In addition more data to support the expiration date proposal should also be provided.

11. It is unclear in vol. 1.7, pg. 134, whether only the 6 and 9 month stability samples from batch PD0335 were evaluated by or if it included samples up to 24 months. It is also unclear whether a new package was opened and used for tablet sampling at each time point. Please clarify these points.

12. A list of samples that will be submitted for methods validation should be provided.

13. There is only one copy of the methods validation package. An additional two copies should be submitted.

14. Three methods validation packages should also be submitted for the drug substance desogestrel. Specifically, the method for related substances, and method for related substances. A list of the samples that will be submitted for method validation should be provided. In addition, a material safety data sheet and a certificate of analysis for the samples should be submitted.

15. Three methods validation packages should be submitted for the drug substance, ethinyl estradiol. Specifically, the method for related substances and method for residual solvents. The method is not the same as the method provided in the USP monograph, therefore it must be validated. The method is in the European Pharmacopia but not the USP therefore, it must also be validated. A list of the samples that will be submitted for method validation should be provided. In addition, a material safety data sheet and a certificate of analysis for the samples should be included.

16. There is a mistake in the Material Safety Data Sheet for desogestrel in vol. 1.9, pg. 470. The molecular formula should be $C_{22}H_{30}O$ not $C_{22}H_{30}O_4$. A Material Safety Data Sheet for ethinyl estradiol is not provided.

17. Deficiencies in the DMF's have been conveyed to the following DMF holders:

18. Comments on labeling will be sent separately. However, the molecular formula and molecular weight of the drug substances must be included in the description section of the package insert.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Christina Kish, Consumer Safety Officer, at (301) 827-4260.

Sincerely

/S/

10/8/97

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:
Orig. NDA
HFD-580
HFD-580/MRhee/DLin/HJolson
HFD-820/ONDC Division Director
HFD-580/CKish/9.29.97/n20713.ir3
concurrence:LPauls 10.3.97/DLin 10.3.97/MRhee 10.3.97

INFORMATION REQUEST (IR)

Kish

NDA 20-713

MAY 6 1997

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

Dear Mr. Mayo:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: CTR-25 (desogestrel and ethinyl estradiol) Tablets

Therapeutic Classification: Standard

Date of Application: April 30, 1997

Date of Receipt: April 30, 1997

Our Reference Number: 20-713

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 29, 1997, in accordance with 21 CFR 314.101(a).

If you have any questions, please contact Christina Kish, Consumer Safety Officer, at (301) 827-4260.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely,

/S/

5/5/97

Lana L. Pauls, M.P.H.
Chief, Project Management Staff
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/HJolson/MRhee/AJordan
DISTRICT OFFICE
HFD-580/CKish/5.5.97/n20713.ak
concurrence:

ACKNOWLEDGEMENT (AC)

NDA 20-713

SEP - 3 1997

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

Dear Mr. Mayo:

Please refer to your pending April 30, 1997, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CTR-25 (desogestrel and ethinyl estradiol) Tablets.

To complete our review of the Clinical, Statistical, and Human Pharmacokinetics and Bioavailability sections of your submission, we request the following information:

Clinical

1. Case report forms (CRF's) for patients who reported pregnancies at the post-treatment follow-up contact should be provided.

2. The following information should be provided for every patient on whom a pregnancy test was performed (see attachment for further details):

    a. Dates of all visits
    b. Dates and results of all pregnancy tests
    c. All tablet-taking information for each subject
    d. Dates of all bleeding or spotting
    e. Whether the pregnancy was considered "in-study" or not
    f. for all subjects found to be pregnant before beginning study drug, whether all study drug was returned
    g. Dates of pregnancy outcome and gestational age at pregnancy outcome determination
    h. Dates and results of any ultrasound exams
    I. Date and reason for discontinuation
    j. Cycles in which barriers were used and type of barriers used

3. A listing that includes all adverse events (AE's) that meet any of the following criteria (see attachment for further details):

    a. serious
    b. related to study drug
    c. related to the reproductive tract

Please indicate whether the AE was the reason for discontinuation and whether the subject was a "starter" or a "switcher."

4. Incidence rates for AE's in total and by "Switchers/Starters" (with pregnancies excluded) should be calculated.

5. For each subject in the endometrial biopsy subset, dates of any bleeding or spotting should be provided.

6. Any additional data you may have addressing the risk of endometrial hyperplasia in subjects receiving CTR-25 should be provided.

7. For subsets, please clarify whether means were calculated using only subjects who had data from each time point. If not, please recalculate.

8. Please indicate where in the submission information concerning withdrawal bleeding is summarized, or provide that summary.

9. Per-cycle rates of breakthrough bleeding, spotting, and bleeding and/or spotting using the following two definitions should be calculated:

    a. Any bleeding and/or spotting that occurs on days 5-21 of the pack or on days 1-4 if preceded by 2 consecutive days of no bleeding/spotting.
    b. Any bleeding and/or spotting during days 1-21 that is not a continuation of withdrawal bleeding (but could include early withdrawal bleeding by your definition).

10. Amenorrhea rates using the definition of no bleeding or spotting during days 1-28 should be calculated.

11. Plasminogen (quantitative) mean values were reported as 0.2 g/L at each of three timepoints: baseline, cycle three and cycle six; however, changes from baseline were reported as 40.9% at cycle 3 and 43.3% at cycle 6, please clarify.

12. Means in addition to medians should be calculated for Table 21, page 0054 of volume 27.

13. Tables 7 and 8 on pages 40 and 41 of Volume 27 do not appear to agree with the table on page 27 of the same volume. Please indicate which subjects were included in each tables cells.

14. An update of pending applications for this product in other countries should be provided.

15. Please provide:

    a. a stratified analysis of your data by both age and race;
    b. a discussion of post-marketing surveillance including the use of Mercilon and adverse events;
    c. CFR tabulations; and
    d. a detailed line listing of pregnancies and the histology subset.

Statistics

1. Please repaginate or revise your index of the statistics section so that the index and page numbers agree with each other.

2. Please provide your submitted data on disk, if possible in SAS or ASCII, include the parameters in the enclosed attachment "Requests for CTR-25."

Clinical Pharmacology

1. The **Pharmacokinetics** subsection of the **CLINICAL PHARMACOLOGY** section of your proposed labeling should be reformatted according to the internal Division guidelines (see enclosed format).

2. Please submit a summary of the human PK/bioavailability section, individual study report summaries and the revised package insert on disk, if possible in WordPerfect 6.1.

3. Raw data of individual studies should be submitted on disk, preferably in ASCII.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

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

Sincerely,

/S/ 9/2/97

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Office Of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES
Internal Division Labeling Guidance
"Requests for CTR-25"

cc:
Orig. NDA
HFD-580
HFD-580/CMauck/ADorantes/VJarugula/LKammerman/MNg/HJolson
HFD-580/CKish/8.5.97/n20713.ir2
concurrence:LPauls 8.13.97/CMauck 8.14.97/LKammerman 8.18.97/VJarugula 8.20.97/ADorantes 8.20.97

INFORMATION REQUEST (IR)

NDA 20-713

NOV 28 97

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

Dear Mr. Mayo:

Please refer to your pending April 30, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CTR-25 (desogestrel and ethinyl estradiol) Tablets.

We have completed our review of your proposed tradename "Desogen-20" and find it unacceptable for the following reason:

> The name Desogen-20 implies that this product is simply a lower dose of your approved drug Desogen. However, the addition of five days of ethinyl estradiol alone constitutes a different dosing regimen. Therefore your proposed tradename is misleading.

Please propose an alternate tradename so that it can be forwarded to the Labeling and Nomenclature Committee for review.

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

Sincerely,

/S/ 11/26/97

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Office Of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Orig. NDA
HFD-580
HFD-580/CMauck/HJolson
HFD-580/CKish/11.20.97/n20713.gc
concurrence:LPauls 11.21.97/CMauck 11.25.97/HJolson 11.25.97

GENERAL CORRESPONDENCE (GC)

KIS/

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 23, 1998 MAR 23 1998

TO: Director, Division of Reproductive and Urologic Drug Products, HFD-580

THROUGH: Lilia Talarico M.D., Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180 LTalarico MM 3-23-98

SUBJECT: NDA 20-713, CTR-25 (Desogestrel and Ethinyl Estradiol)

FROM: Kurt Sizer M.D., Medical Reviewer, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

I. Background

NDA 20-713 for the oral contraceptive CTR-25 (Desogestrel and Ethinyl Estradiol), is presently under review by HFD-580, and includes a pivotal study (086-001), and two smaller studies which assess follicular development and bleeding patterns. Within study 086-001 are 7 substudies, which evaluated the effects of CTR-25 on lipids, other endocrine parameters, endometrial morphology, carbohydrate metabolism, pharmacokinetics, **hemostasis/ fibrinolysis**, and ophthalmologic conditions.

Study 086-001 was an open-label, 33 center, non-comparative, prospective study of the safety and efficacy of CTR-25 of 1250 women completing a minimum of 10,000 cycles, with a minimum of 200 women completing at least 13 cycles. Approximately half the subjects were "starters", i.e. had no OC use in the two months prior to study entry), and half were "switchers", i.e. had switched from another combined OC. Endpoints were 1) contraceptive efficacy, 2) vaginal bleeding patterns, and 3) safety. Seven subsets of subjects were studied for the effects of CTR-25 on lipid profiles (97 subjects), endocrine profiles (64 subjects), endometrial morphology (40 subjects), carbohydrate metabolism (32 subjects), pharmacokinetics (24 subjects), hemostasis and fibrinolysis (99 subjects), and ophthalmologic conditions (55 subjects).

Inclusion criteria included women of 18-50 years of age, regular menses for the 3 months prior to study entry, not pregnant or breast-feeding, but sexually active and at risk for pregnancy, and willing to continue study drug for 18 cycles.

Exclusion criteria included any contraindications to combined OC use (thrombophlebitis or thromboembolic disorders, a past history of DVT or thromboembolic disorders, cerebrovascular or coronary artery disease, known or suspected breast cancer, endometrial or other estrogen-dependent neoplasm, undiagnosed abnormal genital bleeding, cholestatic jaundice of pregnancy or jaundice with prior OC use, hepatic adenomas or carcinomas, and pregnancy), use of an injectable hormonal contraceptive for the past 6 months, use of a progestin-releasing IUD for the past 3 months, use of contraceptive implants for the past 2 months, outside the 80-130% range of ideal body weight, use of lipid-altering drugs or drugs that affect steroid pharmacokinetics in the past 30 days, any prior use of etretinate (a oral retinoid indicated for severe psoriasis), systolic blood pressure of ≥ 150 mm Hg or diastolic blood pressure of ≥ 90 mm Hg, abnormal pelvic, Pap smear, or breast exam findings, significant cardiovascular, hepatic, or renal disease, diabetes or thyroid disorders, consumption of more than two alcoholic beverages per day on average, smoking ≥ 15 cigarettes a day if ≥ 35 years old, a history of drug abuse, or use of an investigational drug within the past 90 days.

A total of 1250 subjects enrolled in study 086-001; 1226 took study drug (48% were starters, 52% were switchers). A total of 663 subjects completed at least 13 cycles, and 327 completed 18 cycles (33% of whom were starters). There were a total of 14050 cycles of study drug exposure.

Eleven subjects conceived during the treatment period. Cumulative life-table estimates were 1.11 pregnancies per 100 woman years of use. A total of 44% of subjects reported drug-related adverse events. Twenty-nine subjects (2.4%) reported a total of 31 serious adverse events. There were no reported deaths, myocardial infarctions, pulmonary emboli, strokes, or deep vein thromboses.

II. Hemostasis/Fibrinolysis Subgroup Study

A subset of 99 subjects from study 086-001, who had NOT used oral contraceptives in the past 2 months prior, were enrolled in the hemostasis/fibrinolysis study. Various laboratory parameters were checked at baseline, after 3 cycles, and after 6 cycles of CTR-25. Subjects were of mean age 30 years, mean weight 65 kg, and mean body mass index of 24 kg/m2. Eighty-four percent of patients were Caucasian, and 10% were Black.

No abnormal values or significant changes from baseline were reported for the Prothrombin Time, Activated Partial Thromboplastin Time, or Fibrinogen, Plasminogen Activator Inhibitor - 1, Tissue Plasminogen Activator, Antithrombin III, or Plasminogen levels. Abnormal values were observed for D-dimer and Factor VII levels however, and our Division has been asked to assess the clinical significance of these.

D-dimer and Factor VII activity values are shown below:

Parameter	Visit	N	Mean	Std Dev
D-dimer (ng/mL)	Baseline	98	612	1445
	Cycle 3	88	884	2628
(Normal <400 ng/mL)	Cycle 6	74	596	2066
Factor VII Activity	Baseline	96	148	73
(%)	Cycle 3	90	162	93
(Normal 65%-135%)	Cycle 6	75	135	72

Details for the specific laboratory assays were not provided by the sponsor.

A. D-dimer Values

Note that the mean D-dimer value is elevated at baseline, and that the differences between D-dimer values after cycle 3, and after cycle 6, compared to baseline are NOT statistically significant (based on the z-test). The mean D-dimer level decreases to the baseline value following 6 cycles of CTR-25, and these overall trends are reflected in the observed fibrin degradation products in this substudy, as shown below:

Profile of FDP Values (% of Subjects)

Fibrin Degradation Products (µg/mL) (Normal = <5 µg/mL)	<5	≤5	≤10	≤20	≤40	≤80
Baseline (N = 97)	81	6	3	3	2	4
Cycle 3 (N = 89)	88	8	2	1	0	1
Cycle 6 (N = 75)	87	8	0	3	3	0

D-dimer values are known to be elevated in the following conditions: diffuse intravascular coagulation, ongoing thrombosis (including pulmonary embolism, deep venous thrombosis, myocardial infarction), peripheral vascular disease, atrial fibrillation (possibly due to intracardiac thrombi), mitral stenosis with intracardiac thrombosis, pregnancy, preeclampsia, liver disease, cancer, after exercise, severe infection, collagen vascular disease, post trauma, postoperatively, congestive heart disease, uremia, age > 60 years, and sickle cell disease. None of the above conditions were identified in patients that were eligible or participated in study 086-001 and the hemostasis/fibrinolysis substudy. Further, D-dimer levels have not been reported to significantly vary during the normal menstrual cycle (Contraception 1997 56 67). However, as is discussed below, the magnitude of the observed D-dimer elevation does not represent a clinically significant prothrombotic state.

Bounameaux P. et. al., (Throm Haemost 1994 71 1), reported the D-dimer results in patients in whom a DVT was clinically suspected. Results are shown below:

Table 1 Characteristics of some commercial assays for D-Dimer

Notation	Commercial name	Producer	Capture Ab	Tagging Ab
ELISA assays				
A	Dimertest		3B6/22	4D2/182
B	Asserachrom DDi		2F7	polyclonal
C	Fibrinostika FaDP		FDP14	FDP DD13
D	D-Dimer micro		monoclonal	polyclonal
Latex assays				
E	Dimertest I		3B6/22	
F	D-dimertest		2F7	
G	Minutex D-Dimer		15C5	
H	FDP-Slidex Direct		monoclonal	

Table 2 Diagnostic performances of plasma measurement of DD (ELISA) in patients clinically suspected of DVT

Study	Assay[1]	Cutoff[2]	n	n(DVT)	Sv	Sp	PPV	NPV
Versus venography								
Heaton (3)	A	400	57	26	100	47	62	100
Rowbotham (4)	A	500	104	45	100	34	54	100
Ott (5)	A	400	108	39	97	65	61	98
Boumameaux (6)	B	500	53	21	95	47	54	94
Chapman (7)	A	400	107	35	89	68	57	92
Moosz (8)	C	500	112	64	98	6	58	75
Weighted average			541	230 (43%)	97.0	47.3	57.6	95.5
95% CI					94.8–99.2	41.8–52.8	52.7–62.5	92.4–98.6
Versus noninvasive diagnosis								
van Bergen (9)	C	540	239	60	92	20	28	88
Elias (10)	B	500	100	45	98	29	53	94
Bones (11)	B	500	116	34	94	51	44	95
Chang-Liem (12)	B	450	32	25	100	29	83	100
Heijboer (13)	B	300	309	70	100	29	29	100
Weighted average			796	234 (29%)	96.6	28.5	36.3	95.4
95% CI					94.4–98.8	24.8–32.2	32.5–40.1	92.2–98.6
Versus all diagnostic methods								
Weighted average			1337	464 (35%)	96.8	35.2	44.3	95.4
95% CI					95.2–98.4	32.0–38.4	41.2–47.4	93.0–97.8

Sv = sensitivity (%); Sp = specificity (%); PPV = positive predictive value (%); NPV = negative predictive value (%); n = number of patients; n(DVT) = number of DVT; 95% CI = 95% confidence interval; [1]after Table 1; [2]expressed in µg/l of fibrinogen-equivalent units (FEU)

Note in the above Table 2, the cutoff D-dimer results are expressed in µg/L (or ng/mL) of fibrinogen-equivalent units. One fibrinogen-equivalent unit is roughly equivalent to 0.5 µg/L of D-dimer units. Thus the D-dimer cutoff results above should be multiplied by 2 to give equivalent D-dimer units.

To summarize the results of the tables above, the sensitivity and specificity of the D-dimer, based on pooled data from 1337 patients with clinically suspected DVT, were 97% and 35%, respectively. Thus, a D-dimer value below a value of 600-1080 ng/mL was determined to rule out a diagnosis of DVT. On the other hand, a D-dimer concentration above the ng/mL range, was not useful to diagnose a DVT, due to the high false-positive rate.

A separate study of the D-dimer (ELISA) measurements in 85 hospitalized patients in whom DVT was clinically suspected, (So Med J 1997 90 907), reported that a value of < 2000 ng/mL ruled out the diagnosis of a DVT, with a sensitivity of 100%, specificity of 59%, positive predictive value of 50%, and negative predictive value of 100%.

The diagnostic value of D-dimer measurements in asymptomatic patients at risk for DVT has been examined in patients undergoing elective abdominal surgery, and in general surgical patients. In a prospective trial of 185 consecutive patients undergoing elective abdominal surgery, who underwent venography on the 8th postoperative day, a plasma D-dimer cutoff of 3000 ng/mL (using assay B in Table 1 above) was determined to distinguish between patients with and without a postoperative DVT, with a sensitivity of 89% and a specificity of 48%.

In a series of 135 general surgical patients (using assay A in Table 1 above), similar results were reported using a D-dimer cutoff of 2400 ng/mL. Further, a preoperative D-dimer value of < 800 ng/mL was associated with the absence of postoperative DVT, with a predictive value of 85%.

In summary, given the baseline elevation of the mean D-dimer, the lack of statistical significance between D-dimer values after cycle 3 and cycle 6 compared to baseline, the numerical trend toward the baseline value following cycle 6, the corroborative trend in fibrin degradation product values, the magnitude of mean D-dimer elevations in the enrolled asymptomatic patients at risk for DVT, and the absence of any thrombotic adverse events reported for study 086-001, a clinically significant drug-related effect of CTR-25 is not suggested by the abnormal D-dimer values reported in the above substudy.

B. Factor VII Values

The Factor VII results during the hemostasis/fibrinolysis substudy, is shown below:

Parameter	Visit	N	Mean	Std Dev
Factor VII Activity (%) (Normal 65%-135%)	Baseline	96	148	73
	Cycle 3	90	162	93
	Cycle 6	75	135	72

Note that the mean Factor VII value is elevated at baseline, returns to within normal range after cycle 6, and that the differences between Factor VII values after cycle 3, and after cycle 6, compared to baseline are NOT statistically significant (based on the z-test).

Plasma Factor VII activity levels increase with age, body mass index, oral contraceptive use (in an estrogen-dependent manner), diabetes, during pregnancy, following menopause, with increasing serum lipids (including cholesterol, triglycerides, HDL and LDL), and in the setting of an acute myocardial infarction or stroke. Further, an increasing number of polymorphisms in the Factor VII gene are being described, which are associated with high circulating Factor VII plasma levels. An increased Factor VII level may be an independent risk factor for ischemic cardiovascular disease (NEJM 1998 338 79). Factor VII levels have not been reported to vary significantly during the normal menstrual cycle (Contraception 1997 56 67).

Based on the eligibility and demographics of the patients that participated in study 086-001 and the hemostasis/fibrinolysis substudy, only oral contraceptive use and increased serum lipids were likely to have contributed to the elevated Factor VII levels observed. It is notable that CTR-25 was noted to increase serum lipids in the lipid profile substudy. Specifically, triglycerides increased by 55% at 3 months, and 60% at 6 months; cholesterol increased 5% at 3 months, and 10% at 6 months; LDL fell 3% at 3 months, and increased 5% at 6 months; HDL fractions increased 9-17% at 3 months, and 13-25% at 6 months; and VLDL rose 58% at 3 months, and 53% at 6 months. Thus, although CTR-25 may have increased Factor VII levels due to its effects on serum lipids, the mean increase of Factor VII activity at baseline, and return to within the normal range after 6 cycles, remains unexplained.

In summary, given the (relatively small) elevation of the mean Factor VII level at baseline, the lack of statistical significance between Factor VII values after cycle 3 and cycle 6 compared to baseline, and the return of Factor VII levels to within the normal range following cycle 6, a clinically significant drug-related effect of CTR-25 is not suggested by the abnormal Factor VII values reported in the above substudy.

/S/ 3/23/98

Kurt Sizer, M.D.

cc:
HFD-180
HFD-180/LTalarico K 3-27-98
HFD-180/KSizer
HFD-181/CSO Consult File
f/t 3/23/98 jgw
MED\C\20713803.0KS

EXCLUSIVITY SUMMARY for NDA # 20-713 SUPPL #_____

Trade Name Mirena **Generic Name** levonorgestrel and ethinyl estradiol
Applicant Name Organon Inc **HFD-** 570

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES /✓/ NO /__/

   b) Is it an effectiveness supplement?

   YES /__/ NO /✓/

   If yes, what type? (SE1, SE2, etc.) ____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /✓/ NO /__/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA #_____ Drug Name_____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /✓/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-071 Desogen

NDA # 20-301 Ortho-Cept

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /__/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /__/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /✓/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /✓/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /✓/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 96001

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /✓/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /✓/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # 96001

Investigation #_, Study # _____

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # ____ YES /✓/ NO /___/ Explain: ____

_____

Investigation #2

IND # ____ YES /___/ NO /___/ Explain: ____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____

_____

Investigation #2.

YES /___/ Explain _____ NO /___/ Explain _____

_____

_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓/

If yes, explain: _____

_____

_____

_____

/S/

_____ 3/20/96

Signature Date

Title: Doc/PM

/S/

_____ 4/20/96

~~Signature~~ of Division Director Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac