CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-683

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

FEB 27 1997

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

NDA 20-683

Alesse™ Tablets
Levonorgestrel 100 µg/Ethinyl Estradiol 20 µg
Wyeth-Ayerst
Philadelphia, PA

SUBMISSION DATES: March 27, 1996
December 20, 1996
January 15, 1997
January 30, 1997
February 20, 1997

REVIEWER: Angelica Dorantes, Ph.D.

TYPE OF SUBMISSIONS: Original NDA and 4 Amendments **Code: 3S**

SYNOPSIS:

An original NDA 20-489 for Alesse™ (levonorgestrel 100 µg/ethinyl estradiol 20 µg) tablets was submitted on March 27, 1996 by Wyeth Ayerst. Alesse™ is a low-dose formulation of levonorgestrel and ethinyl estradiol indicated for the prevention of pregnancy and is proposed for marketing in standard 21-day and 28-day (7 days of placebo) regimens. The pharmacokinetics of the to-be-marketed Alesse™ Tablets, were characterized in one single/multiple dose study (No. 0858A-101-US; Report GMR-26525) conducted in the target population, premenopausal women. The overall results showed that levonorgestrel, unbound-levonorgestrel, and ethinyl estradiol increased from day 1 to day 21 by 96%, 83%, and 19%, respectively, indicating that levonorgestrel and ethinyl estradiol accumulate after multiple doses.

On January 15, 1997, the sponsor submitted an amendment to NDA 20-683 including their response to an Agency's request for additional information. FDA asked if they had performed a study comparing the bioavailability of levonorgestrel/ethinyl estradiol tablets with that of a reference solution or comparator product. The sponsor responded that they did not conduct such a bioavailability study for Alesse™. They felt that such a study was not needed because Alesse™ formulation is proportionally similar to the marketed product, Triphasil®; the only differences among the core tablets are the amounts of the active ingredients, and corresponding slight differences in the amounts of lactose. They provided supportive bioavailability information for the three formulations of Triphasil®, which shows that the relative bioavailability of levonorgestrel and ethinyl estradiol, as compared to an oral reference solution, is about 90-100% for both compounds. In addition, on February 20, 1997, the sponsor officially requested a waiver

for the CFR 320.21 requirement of the submission of *in vivo* bioavailability data for Alesse™ tablets.

On January 30, 1997, a chemistry, manufacturing and controls amendment was submitted to the Agency, in response to an FDA request for additional information. FDA asked whether the sponsor had **i)** performed chemical testing to characterize placebo tablets that had faded due to light exposure, **ii)** whether the wallets (intended for use by the patient to protect the product from light) had been used in clinical trials, and **iii)** whether the migration of from the wallets into Alesse tablets could potentially affect the absorption of the active ingredients. The sponsor responded that the placebo tablets are exactly the same as those included with the marketed product, Triphasil®, and these placebo tablets, and their corresponding packing and labeling were approved by FDA on March 9, 1993 and had been used in Triphasil® since mid-1994. The sponsor also included dissolution data for Alesse™ tablets that were exposed to, and absorbed, quantities of far in excess of those seen in the stability studies. The dissolution results showed that the has no impact on the release of the active ingredients from Alesse™ tablets, nor does absorption of affect the *in vitro* product's potency or purity (see detail information in Attachment I).

II. RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed NDA 20-683 for Alesse™ tablets that was submitted on March 27, 1996. Based on the review of the overall information included in this submission, OCPB/DPEII is of the opinion that **i)** the provided analytical and pharmacokinetic data, and **ii)** the proposed *in vitro* dissolution method (USP Apparatus 2, 75 rpm, Medium: polysorbate 80 [5PPM] in water; 500 mL) and release specifications (Q=[redacted]% at [redacted] minutes for levonorgestrel and ethinyl estradiol), are appropriate and acceptable.

With respect to the sponsor request of a waiver for the requirement of the submission of *in vivo* bioavailability data for Alesse™, OCPB/DPEII is of the opinion that the supportive information is appropriate and based on CFR 320.22 (d)(2) the requested bio-waiver for Alesse™ is granted.

Regarding the package insert, on December 20, 1996 Wyeth-Ayerst submitted an updated version of their proposed package insert for Alesse™. After review of the information included in the Pharmacokinetic section of the labeling, OCPB/DPEII recommends that the changes proposed on pages 14 to 17 of this bio-review be incorporated into the labeling.

Lastly, regarding the issue of a possible interaction between levonorgestrel/ethinyl estradiol and the provided dissolution data are informative but do not address the Agency's concern of a possible *in vivo* Alesse interaction (due to the potential migration of from the wallets into Alesse™) that may affect the bioavailability of the active ingredients and their efficacy. Therefore, the reviewing disciplines (clinical, biopharm, and chemistry) of this submission are of the opinion that the sponsor should conduct a bioequivalence study comparing the rate and extent of absorption of Alesse™ active ingredients (levonorgestrel and ethinyl estradiol) using wallets for 21 days (as the proposed to-be-marketed product) and without the wallets (as used in the PK and clinical studies). However, due to the fact that there is background information for the marketed Triphasil® product using the same wallets, OCPB considers that the recommended bioequivalence study may be conducted as a Phase IV study, but the study results should be submitted for review within 6 to 9 month of approval date.

Please convey the Recommendation and Labeling Comments as appropriate to the sponsor.

NOTE: Attachments I to III are being retained in OCPB and may be obtained upon request.

A Dorantes 2/26/97

Angelica Dorantes, Ph.D.
Division of Pharmaceutical Evaluation II

RD Initialed by John Hunt. JPH 2/ 23 /97

FT Initialed by John Hunt. 2/27/97

cc: NDA 20-683, HFD-580 (Price, Kish), HFD-870 (Chen, Dorantes), HFD-850 Millison (for Drug).

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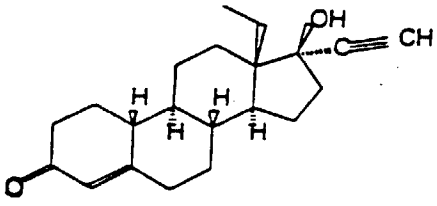
III. BACKGROUND

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation). Oral formulations combining an estrogen and a progestin have been used to provide effective contraception for more than a quarter of a century. In 1982, FDA approved NDA 18,668 for Nordette (LNG 180 µg/EE 30 µg), a Wyeth-Ayerst oral contraceptive product that combined EE and LNG (the biologically active enantiomer [l-isomer] of norgestrel). In the present submission, Wyeth-Ayerst proposes for marketing Alesse™, a low-dose oral contraceptive product containing LNG and EE.

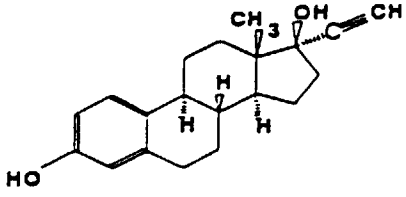
Levonorgestrel and ethinyl estradiol are USP monograph items that are commercially available. Their molecular weight, empirical formula, and chemical structure are described below.

LEVONORGESTREL



$C_{21}H_{28}O_2$ MW: 312.45

ETHINYL ESTRADIOL



$C_{20}H_{24}O_2$ MW: 296.41

IV. DRUG FORMULATION

The proposed to-be-marketed formulation was used in all pharmacokinetic and clinical studies. Table 1 provides the information concerning the batch number, batch size, formulation number, manufacturer, etc.

TABLE 1

Study No.	*Batch No*	*Batch Size*	*Formulation*	*Manufacturer*	*Date*	*Amount Assayed*
858A-101-US	A93D033		0930271C	Wyeth-Ayerst Pharmaceuticals Guayama, PR	June 1993	LNG: 103 µg/tab EE: 21 µg/tab

*Production Size Batch

Only one strength of the combined progestin/estrogen (LNG 100 µg/EE 20 µg) product is proposed for marketing. Alesse™ is a round pink, biconvex immediate release, aqueous film-coated tablet with "W" debossed on one side and "912" debossed on the other. Table 2 includes the formulation of the LNG/EE 100/20 µg tablets proposed to-be-marketed.

TABLE 2

Active Ingredients	*Input/Tablet*
Levonorgestrel, USP	[redacted]mg*
Ethinyl Estradiol, USP	[redacted] mg*
	* Input includes a [redacted]% overage to compensate for manufacturing losses
Inactive Ingredients Core Tablet	
[redacted] Cellulose, NF	mg
Lactose, NF monohydrate	mg
Polacrilin potassium, NF	mg
Magnesium stearate, NF	mg
Theoretical Core Tablet Weight	[redacted]mg
Coating	
Polyethylene glycol NF	[redacted]mg
Wax E	[redacted] mg
	[redacted]mg
Theoretical Coated Tablet Weight	[redacted]mg

The 21-day regimen consists of 1 active tablet taken daily for 21 days. The 28-day regimen consists of 1 active tablet taken daily for 21 days, followed by 1 placebo tablet taken daily for 7 days. The placebo is a round, green biconvex tablet with "W" debossed on one side and "650" on the other.

V. *IN VITRO* METHODOLOGY

The proposed dissolution method is presented in Table 3.

TABLE 3

PROPOSED DISSOLUTION METHOD AND SPECIFICATIONS FOR ALESSE™ TABLETS	
Dosage Form:	Levonorgestrel/Ethinyl Estradiol Tablet
Strength(s):	100 µg levonorgestrel and 20 µg ethinyl estradiol
Apparatus Type:	USP Apparatus 2
Media:	[redacted]ppm polysorbate[redacted] in distilled water at [redacted]°C
Volume:	[redacted]mL
Speed of Rotation:	[redacted] rpm
Sampling Time(s):	[redacted]minutes
Analytical Method:	
Release Rate Specifications:	NLT[redacted]% (Q) for both LNG and EE

Table 4 presents a summary of the *in vitro* release test results for the lot used in the pivotal pharmacokinetic study.

TABLE 4

Study No.	Batch No.	Component	Sampling Times	% Dissolved Range	% Dissolved Mean	% CV
858A-101-US	A93D033	Levonorgestrel	min		83.6	2.9
			min		90.9	2.6
			min		94.7	1.9
			min		96.5	2.0
		Ethinyl Estradiol	min		103.9	1.3
			min		103.3	1.8
			min		103.2	2.1
			min		103.4	1.8

COMMENT:

It should be noted that the proposed *in vitro* dissolution test is the same as the one described in *the 23 USP Official Monograph for Levonorgestrel and Ethinyl Estradiol Tablets.* However, the proposed specifications (Q=[redacted]% at [redacted]minutes for both, LNG and EE) are different to those described in the USP (Q=[redacted]% at [redacted]min and Q=[redacted]% at [redacted]minutes for LNG and EE, respectively).

VI. ANALYTICAL METHODOLOGY

Serum samples for levonorgestrel were assayed by and the minimum quantifiable concentration (MQC) was pg/mL. Serum samples for EE were assayed by pg/mL. The sex hormone binding globulin (SHBG) concentrations in serum were determined by The method had a lower limit of quantitation of nmol/L and spanned a range of nmol/L.

Protein binding of levonorgestrel was determined by using equilibrium dialysis at [redacted]°C with a stainless steel dialysis block in which a [redacted] dialysis membrane separates each pair of [redacted] mL cells.

Table 5 presents a summary of the analytical methods used for the bio-study, and the MQC and standard curve ranges of the assys for LNG, EE and SHBG.

TABLE 5

Study No.	Analyte	Biologic Fluid	Method	Minimum Quantifiable Conc	Calibration Curve Range
101	LNG	Serum		62.5 pg/mL	pg/mL
101	EE	Serum		2 pg/mL	pg/mL
101	SHBG	Serum		6.25 nmol/L	nmol/L

COMMENT:

The validations for the analytical methodologies used for the determination of LNG, EE, SHBG and protein binding are adequate.

VII. PHARMACOKINETIC STUDIES

The pharmacokinetic characteristics of the to-be-marketed product were characterized in one bio-study No. 0858A-101-US conducted in 22 women (see details of this study in Attachment II).

1. BIOAVAILABILITY/BIOEQUIVALENCE:

a). ***Absolute Bioavailability:*** No absolute bioavailability information was submitted. However, literature information indicates that after oral administration LNG is rapidly and completely absorbed (bioavailability %) and it is not subject to first-pass metabolism. EE is rapidly absorbed from the gastrointestinal tract, but due to marked metabolism in the gut mucosa and during passage through the liver, EE absolute bioavailability is about %. Absorption appears to take place in the small bowel since the bioavailability of EE is not reduced in patients with ileostomy.

b). ***Relative Bioavailability:*** A study comparing the bioavailability of Alesse™ with that of a reference or comparator product was not conducted. However, the sponsor refers to three bioavailability studies (Nos. 14876, 15410, and 14720) that were conducted for their marketed levonorgestrel/ethinyl estradiol product, Triphasil®. The sponsor mentioned that a bioavailability study was not conducted because the Alesse™ formulation is proportionally similar to the marketed product, Triphasil; the only differences among the core tablets are the amounts of the active ingredients and the corresponding slight differences in the amounts of lactose (see Table 6).

Triphasil bioavailability studies' Nos. 14876, 15410, and 14720 were submited on April 21, 1988 under Supplement (S-014) to NDAs 19-190 and 19-192 for Triphasil and were approved by FDA on August

15, 1991. These studies showed that the relative bioavailability of levonorgestrel and ethinyl estradiol, as compared to an oral reference solution, was 1% for both compounds (see Attachment II). A cross-study comparison of these studies is included in Table 7. The results showed that mean pharmacokinetic parameters obtained with Alesse formulation are similar to those observed with Triphasil, once corrected for dosage differences.

TABLE 6. Comparison of Ingredient Amounts in mg/Tablet

Ingredient	Triphasil® 125/30 µg	Triphasil® 50/30 µg	Triphasil® 75/30 µg	Alesse™ 100/20 µg
Active				
4% Levonorgestrel Trituration				
2% Ethinyl Estradiol Trituration				
Inactive Core Tablet				
cellulose, NF				
Lactose, NF, monohydrate powder				
Magnesium Stearate, NF				
Polacrilin Potassium, NF				
Total Core Weigth				
Coating				
Polvethvlene Clvcol. 1450. NF				
Wax E				
Total Weigth Coated Tablets				

TABLE 7. Comparison of LNG and EE Pharmacokinetic Parameters

Compoun	Study No. LNG/EE dos	Formulati	Cmax (ng/mL)	Tmax (h)	AUC (ng/mL*h	Cmax,co (ng/mL)	AUCcor* (ng/mL*h	Fr** (%)
LNG	**26525** *(1x100/20)*	Alesse™	2.8	1.6	35	2.8	35	-
		-	-	-	-	-	-	
	14876 *(2x50/30)*	Triphasil Solution	3.4	1.3	34	3.4	34	112
			4.2	0.7	31	4.2	31	
	15410 *(2x125/30)*	Triphasil Solution	5.0	1.6	67	2.0	27	105
			7.7	0.8	64	3.1	26	
	14720 *(2x75/40)*	Triphasil Solution	4.1	1.5	42	2.7	28	115
			5.5	0.8	37	3.7	25	
			(pg/mL)	(h)	(pg/mL*h)	(npg/mL)	(npg/mL*h	(%)
EE	**26525** *(1x100/20)*	Alesse™	62	1.5	635	62	653	-
		-	-	-	-	-	-	
	14876 *(2x50/30)*	Triphasil Solution	281	1.4	2251	93	743	91
			338	1.0	2499	112	825	
	15410 *(2x125/30)*	Triphasil Solution	229	1.5	2144	76	708	93
			299	1.0	2278	99	752	
	14720 *(2x75/40)*	Triphasil Solution	358	1.6	4354	90	1089	109
			436	1.2	4226	109	1057	

COMMENT:

Despite the fact that the sponsor did not provide bioavailability information for Alesse (i.e., compared to a reference standard), the bioavailability information for Triphasil appears to be adequate to support a bio-waiver of the requirement of bioavailability data for this NDA.

c). ***Bioequivalence:*** No bioequivalence studies were submitted. The to-be-marketed formulation/product was used in the pharmacikinetic and clinical studies.

d). ***Food Effect:*** The effect of food in the bioavailability of Alesse™ was not studied.

e). ***Dose Proportionality:*** No dose proportionality studies were conducted. Only one dose level will be recommended in the package insert.

2. PHARMACOKINETICS:

The pharmacokinetic characteristics of Alesse™ were only evaluated in study No. 0858-A-101-US.

a). *Single and Multiple Dose:*

Study No. 0858-A-101-US was an open label, multiple-dose trial, where the objective was to evaluate single and multiple dose pharmacokinetics of levonorgestrel and ethinyl estradiol. Twenty two subjects were enrolled and received LNG 100µg/EE 20 µg as an oral monophasic single-tablet regimen. Blood samples were collected at 0, 1, 2, 4, 7, 12, 16, and 24 hours after dose administration on days 1, 6, and 21. Samples were also collected 48 and 72 hours after the last oral dose (day 21). Additional blood samples were collected for SHBG concentrations and total protein binding analysis. Levonorgestrel serum samples were analyzed by and ethinyl estradiol serum samples by methods were used to estimate PK parameters of LNG amd EE. Analysis of variance (ANOVA) was used to determine any statistically significant differences in serum concentrations and PK parameters among days 1, 6, and 21. Pairwise comparisons between the days were made by using at a significance level of

Figure 1 illustrates mean±SD LNG and EE serum concentrations vs. time and Table 8 includes levonorgestrel, unbound levonorgestrel, and ethynyl estradiol pharmacokinetic parameters in 22 healthy female subjects receiving oral 100 µg LNG/20 µg EE doses every 24 hours.

The results showed that levonorgestrel AUC increased from day 1 (single dose) to days 6 and 21 (multiple doses) by 34% and 96%, respectively. Unbound-levonorgestrel AUC increased from day 1 to days 6 and 21 by 25% and 83%, respectively. Ethinyl estradiol did not accumulate from day 1 to

FIGURE 1

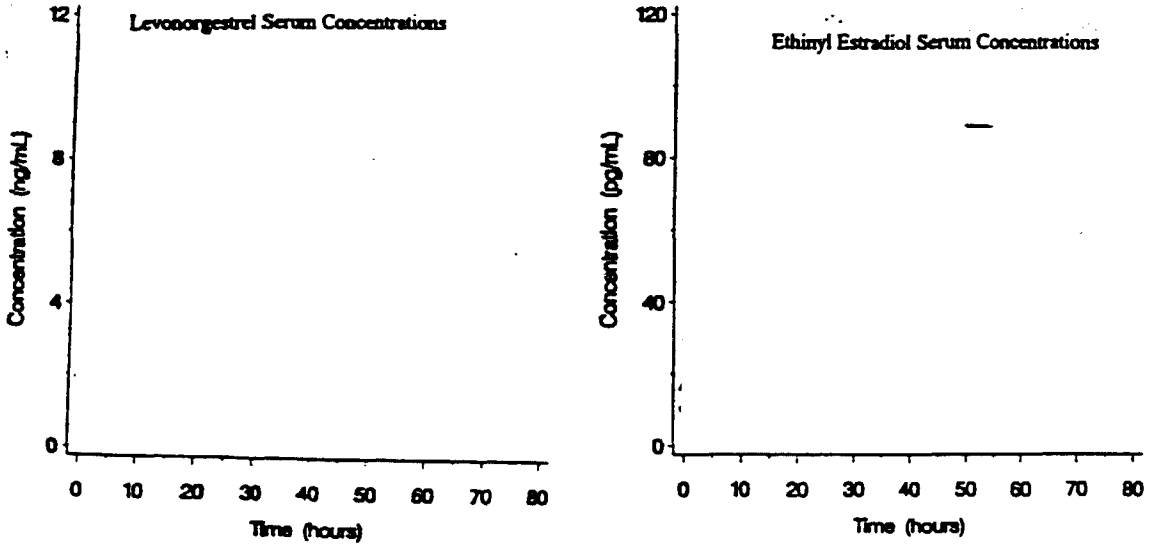


TABLE 8

Day	Cmax ng/mL	Tmax (h)	AUC ng/mL*h	CL/F mL/h/kg	Vlz/F L/kg	SHBG nmol/L
Levonorgestrel						
1	2.75 (0.88)	1.6 (0.9)	35.2 (12.8)	53.7 (28.8)	2.66 (1.09)	57 (18)
6	4.52 (1.79)	1.5 (0.7)	46.0 (18.8)	40.8 (14.5)	2.05 (0.86)	81 (25)
21	6.00 (2.65)	1.5 (0.5)	68.3 (32.5)	28.4 (10.3)	1.43 (0.62)	93 (40)
Stat Test*	1<6<21	-	1<6<21	1>6>21	1>6>21	1<6<21
Unbound-Levonorgestrel						
	pg/mL	h	pg/mL*h	mL/h/kg	mL/kg	nmol/L
1	51.2 (12.9)	-	654 (201)	2.79 (0.97)	135.9 (41.8)	1.92 (0.30)
6	77.9 (22.0)	-	794 (240)	2.24 (0.59)	112.4 (0.5)	1.80 (0.24)
21	103.6 (36.9)	-	1177 (452)	1.57 (0.49)	78.6 (29.7)	1.78 (0.19)
Stat Test*	1<6<21	-	1<6<21	1>6>21	1>6>21	1<6=21
Ethinyl Estradiol						
	pg/mL	h	pg/mL*h	mL/h/kg	mL/kg	nmol/L
1	62.0 (20.5)	1.5 (0.5)	653 (227)	567 (204)	14.3 (3.7)	-
6	76.7 (29.9)	1.3 (0.7)	604 (231)	610 (196)	15.5 (4.0)	-
21	82.3 (33.2)	1.4 (0.6)	776 (308)	486 (179)	12.4 (4.1)	-
Stat Test*	1>6=21	-	1=6<21	1=6>21	1=6>21	-

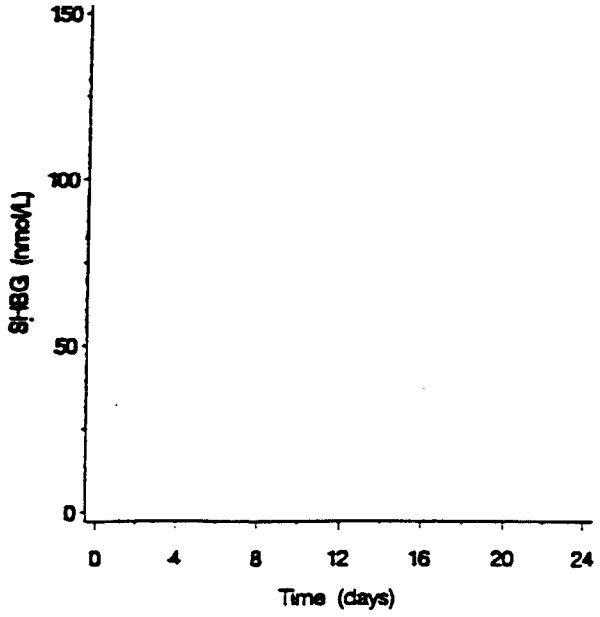
*Duncan's multiple range (p=0.05)

day 6, however, it did accumulate slightly (by 19%) over the course of multiple-dose adminstration from day 1 to 21. The increase in ethinyl estradiol AUC from day 1 to day 21 was consistent with a compound that has a half-life of 18 hours. In conclusion, the results of this study indicate that LNG and EE accumulate after multiple doses.

3. PROTEIN BINDING:

LNG binds almost exclusively to sexual hormone binding globulin (SHBG). EE is 97% bound to plasma albumin. EE does not bind to SHBG but induces SHBG synthesis. In the above study, SHBG appeared to increase linearly from days 1 to 12 than remained at stable levels from days 12 to 21 (Figure 2).

FIGURE 2



Total LNG concentrations increased over 21 days but maximum free LNG concentrations were achieved after 11 days or when SHBG concentrations reach a plateau of about nmol/L. The difference in accumulation between total LNG and unbound-LNG is due to the increase in EE-induced SHBG. This implies that the increased amounts of SHBG were able to bind more LNG, thus resulting in a greater increase in total LNG than free LNG. Because of a decrease in the fraction of unbound drug, the accumulation of unbound-LNG was approximately % less than LNG.

4. SPECIAL POPULATIONS:

No special population studies were submitted. The PK and clinical studies were conducted in the target population, premenopausal women.

5. DRUG METABOLISM:

No metabolic studies were submitted for review. However, a significant body of literature is available on the metabolism of ethinyl estradiol (17a-ethynylestradiol) and levonorgestrel.

Levonorgestrel: The most important metabolic pathway occurs in the reduction of the group and at positions followed by Most of the metabolites that circulate in the blood are while excretion occurs predominantly in the form of Some of the parent also circulates as Metabolic clearance rates may differ among individuals by severalfold, and this may account in part for the high variability observed in levonorgestrel concentrations among users.

Ethinyl Estradiol: The metabolic pathways of ethinyl estradiol are summarized in Figure 3. are responsible for the that is the major oxidative reaction. The is further transformed by prior to urinary and fecal excretion. Levels of vary widely among individuals and can explain the variation in rates of Ethinyl etradiol is excreted in the urine and faeces as and undergoes circulation.

FIGURE 3

6. DRUG INTERACTIONS:

No drug-drug interaction studies were submitted for review. However, there are in the literature many publications that indicate that several possible interactions between ethinyl estradiol and other drugs may occur.

Pharmacological interactions between ethinyl estradiol and other compounds may be of two kinds. 1) Drug(s) may decrease the effectiveness of EE to cause breakthrough bleeding or to allow pregnancy to occur. In a few other cases EE levels may be enhanced, increasing side-effects. 2) EE may interfere with the metabolism of other compounds. In general, interactions of the first kind are due to interference with the absorption, metabolism or excretion of EE, and interactions of the second type are due to competition for metabolic pathways.

- *Absorption interactions:* Infective diarrhea may induce failure of ethinyl estradiol by increasing gastrointestinal motility and reducing hormone absorption. Therefore, any drugs which reduces gut transit and causes diarrhea is potentially likely to reduce concentrations of ethinyl estradiol.
- *Interactions with metabolism:*

  Gastrointestinal Wall: The sulphation of ethinyl estradiol in the gastrointestinal wall has been shown to be a site of interaction for the enhancement of the activity of this drug and may increase its bioavailability and side-effects. (i.e., ascorbic acid acts as competitive inhibitor for sulphation in the gastrointestinal wall increasing ethinyl estradiol bioavailability about 50%).

  Hepatic Metabolism: The most clinically significant group of interactions occurs with other drugs that may induce ethinyl estradiol microsomal enzymes and may decrease ethinyl estradiol plasma levels below contraceptive protection levels, increasing the risk of pregnancy while taking these agents (i.e., anticonvulsant agents: phenytoin, primidone, barbiturates, carbamazepine, ethosuximide, and methosuximide; antituberculous drugs as rifampicin; antifungal drugs as griseofulvin, etc.).
- *Interference with enterohepatic circulation:* Ethinyl estradiol conjugates are excreted in the bile and may be broken down by gut bacteria in the colon to liberate the active hormone which can then be reabsorbed. However, there are clinical reports who support the view that enterohepatic circulation of ethinyl estradiol decreases in women taking antibiotic agents such as ampicillin, tetracycline, etc. and these women may become pregnant while taking these antibiotics.
- *Interference in the Metabolism of Other Drugs:* Ethinyl estradiol inhibits hepatic microsomal enzymes and may interfere in the metabolism of other drugs. In this way it may slow the metabolism of other drugs, increasing their plasma and tissue concentrations and increasing the risk of side-effects (i.e., analgesic anti-inflammatory drugs; antypirin, antidepressant agents, cyclosporin, theophylline, ethanol, etc.). In addition, estrogens appear to have the capacity to induce hepatic drug conjugation, particularly glucuronidation. This will have the opposite pharmacokinetic effect to the inhibitory action on hydroxylation.

Drugs which decrease OCS concentrations
Antibiotic agents
Anticonvulsant agents
Griseofulvin
Purgatives
Rifampicin

Drugs which have their concentrations decreased by OCS
Aspirin
Clofibric acid
Lorazepam
Morphine
Oxazepam
?Paracetamol
Pethidine
Temaxepam

Drugs which have their concentrations increased by OCS
Aminopyrine
Antipyrine
Chlordiazepoxide
Corticosteroid agents
Diazepam
Imipramine
Metoprolol
Nitrazepam
Theophylline
Triazolam
Vitamin A
?Vitamin D

7. PK/PD RELATIONSHIPS AND POPULATION PHARMACOKINETICS:

No information on PK/PD relationships and population PK was submitted.

VIII. PROPOSED LABELING

Regarding the package insert for Alesse™, on December 20, 1996, the sponsor submitted an updated version of the labeling which incorporated

The proposed package insert is included in Attachment III

LABELING COMMENT:

FIGURE 1

Mean(SD) levonorgestrel and ethinyl estradiol serum concentrations in 22 subjects receiving Alesse (100 µg levonorgestrel and 20 µg ethinyl estradiol).

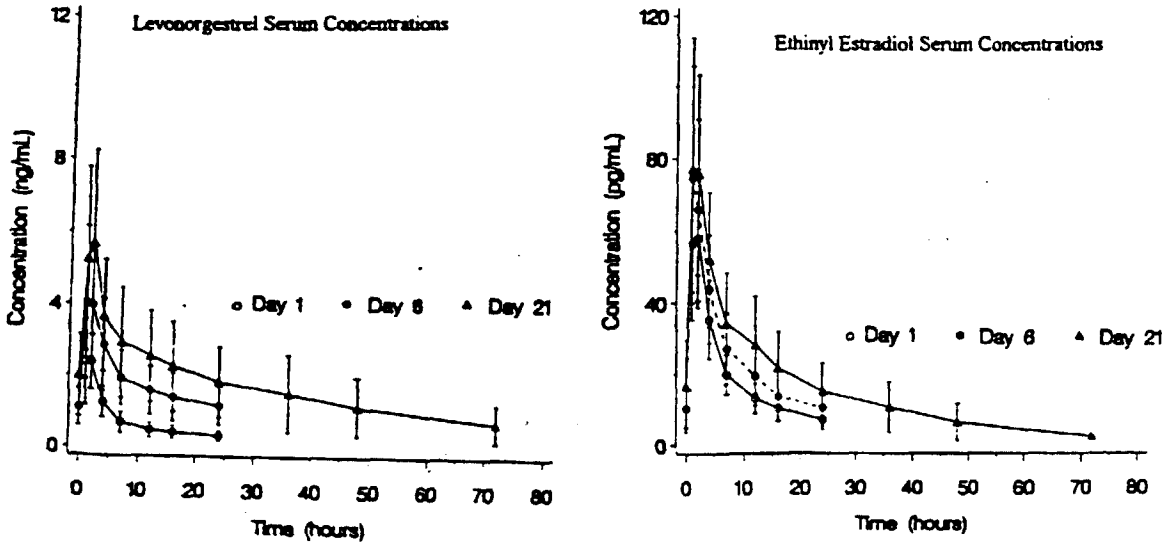


Table 1 provides a summary of the levonorgestrel and ethinyl estradiol pharmacokinetic parameters.

TABLE 1

Mean (SD) Pharmacokinetic Parameters of Alesse Over a 21 Day Dosing Interval

Day	Cmax ng/mL	Tmax (h)	AUC ng/mL*h	CL/F mL/h/kg	Vlz/F L/kg	SHBG nmol/L
Levonorgestrel						
1	2.75 (0.88)	1.6 (0.9)	35.2 (12.8)	53.7 (28.8)	2.66 (1.09)	57 (18)
6	4.52 (1.79)	1.5 (0.7)	46.0 (18.8)	40.8 (14.5)	2.05 (0.86)	81 (25)
21	6.00 (2.65)	1.5 (0.5)	68.3 (32.5)	28.4 (10.3)	1.43 (0.62)	93 (40)
Unbound-Levonorgestrel						
	pg/mL	h	pg/mL*h	mL/h/kg	mL/kg	nmol/L
1	51.2 (12.9)	-	654 (201)	2.79 (0.97)	135.9 (41.8)	1.92 (0.30)
6	77.9 (22.0)	-	794 (240)	2.24 (0.59)	112.4 (0.5)	1.80 (0.24)
21	103.6 (36.9)	-	1177 (452)	1.57 (0.49)	78.6 (29.7)	1.78 (0.19)
Ethinyl Estradiol						
	pg/mL	h	pg/mL*h	mL/h/kg	mL/kg	nmol/L
1	62.0 (20.5)	1.5 (0.5)	653 (227)	567 (204)	14.3 (3.7)	-
6	76.7 (29.9)	1.3 (0.7)	604 (231)	610 (196)	15.5 (4.0)	-
21	82.3 (33.2)	1.4 (0.6)	776 (308)	486 (179)	12.4 (4.1)	-

Distribution

Levonorgestrel in serum is primarily bound to SHBG. Ethinyl estradiol is about 97% bound to plasma albumin. Ethinyl estradiol does not bind to SHBG but induces SHBG synthesis.

Metabolism

Levonorgestrel: The most important metabolic pathway occurs in the reduction of the group and at positions followed by Most of the metabolites that circulate in the blood are while excretion occurs predominantly in the form of glucuronides. Some of the parent levonorgestrel also circulates as Metabolic clearance rates may differ among individuals by severalfold, and this may account in part for the high variability observed in levonorgestrel concentrations among users.

Ethinyl Estradiol: . . in the liver are responsible for the that is the major oxidative reaction. The metabolite is further transformed by prior to urinary and fecal excretion. Levels of vary widely among individuals and can explain the variation in rates of ethinyl estradiol Ethinyl etradiol is excreted in the urine and faeces as glucuronides and sulphates and undergoes enterohepatic circulation.

Excretion and ***Special Populations*** *(Race, Hepatic Insufficiency,* and *Renal Insufficiency)*
Sponsor's proposed information is appropriate.

Drug-Drug Interactions

No specific drug-drug interaction studies for Alesse were conducted but there are many publications that indicate that interactions between ethinyl estradiol and other drugs may occur.

- *Absorption interactions:* Infective diarrhea may induce failure of ethinyl estradiol by increasing gastrointestinal motility and reducing hormone absorption. Therefore, any drugs which reduces gut transit and causes diarrhea is potentially likely to reduce concentrations of ethinyl estradiol.
- *Interactions with metabolism:*

  Gastrointestinal Wall: Sulphation of ethinyl estradiol has been shown to occur in the gastrointestinal (GI) wall . Therefore, drugs which act as competitive inhibitors for sulphation in the GI wall may increase ethinyl estradiol bioavailability and side-effects. (i.e., Ascorbic acid)

  Hepatic Metabolism: The most clinically significant group of interactions occurs with drugs that induce ethinyl estradiol microsomal enzymes that can decrease ethinyl estradiol concentrations below contraceptive protection levels, increasing the risk of pregnancy while taking them (i.e., anticonvulsant agents; phenytoin, primidone, barbiturates, carbamazepine, ethosuximide, and methosuximide; antituberculous drugs as rifampicin; antifungal drugs as griseofulvin, etc.).
- *Interference with enterohepatic circulation:* Some clinical reports support the view that enterohepatic circulation of estrogens decreases when antibiotic agents such as ampicillin, tetracycline, etc. are given, increasing the risk of pregnancy while taking these antibiotics.
- *Interference in the Metabolism of Other Drugs:* Ethinyl estradiol inhibits hepatic microsomal enzymes that may interfere in the metabolism of other drugs. In this way ethinyl estradiol may slow the metabolism of other drugs, increasing their plasma and tissue concentrations and increasing the risk of side-effects (i.e., analgesic anti-inflammatory drugs; antypirin, antidepressant agents, cyclosporin, theophylline, ethanol, etc.). In addition, estrogens appear to have the capacity to induce hepatic drug conjugation, particularly glucuronidation. This will have the opposite pharmacokinetic effect to the inhibitory action on hydroxylation.