CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-864

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-864**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**May 27, 2005, original submission**
	August 22, 2006, resubmission
	December 22, 2006 major amendment
PRODUCT:	**Levonorgestrel (90 µg) /**
	Ethinyl Estradiol (20 µg) Continuous Use
INTENDED CLINICAL POPULATION:	**For contraceptive use in women**
SPONSOR:	**Wyeth Pharmaceuticals**
DOCUMENTS REVIEWED (original submission):	**Module 2: Common Technical Document**
	Summaries. 2.4 Nonclinical Overview
REVIEW DIVISION:	**Division of Reproductive and Urologic Products**
	(HFD-580)
PHARM/TOX REVIEWER:	**Leslie McKinney, Ph.D.**
PHARM/TOX SUPERVISOR:	**Lynnda Reid, Ph.D.**
DIVISION DIRECTOR (Acting):	**Scott Monroe, M.D.**
PROJECT MANAGER:	**John Kim, R.Ph., J.D.**

Date of review submission to Division File System (DFS): 3-20-07

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

This Dec. 22, 2006 amendment was filed to address chemistry and manufacturing (CMC) issues for the continuous use contraceptive Lybrel. There were no new nonclinical studies submitted for this amendment. Based on previously submitted nonclinical data for levonorgestrel (LNG) and ethinyl estradiol (EE), from a Pharmacology / Toxicology perspective the LNG 90 µg/EE 20 µg dosage in the continuous use regimen can be approved.

B. Recommendation for nonclinical studies

At a guidance meeting held April 8, 2002, DRUP indicated to Wyeth that nonclinical studies performed to support marketed LNG/EE products were sufficient to support the proposed continuous use regimen. Therefore, no new nonclinical studies were carried out in support of the original submission, the resubmission, or for this amendment.

C. Recommendations on labeling

There are no Pharm/Tox recommendations for changes in the proposed labeling for LNG/EE combination oral contraceptives.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

There were no new nonclinical studies submitted in support of this application. Levonorgestrel is a 'third generation' synthetic progestin that has been widely used in many types of oral contraceptives. Its toxicological profile is well understood across species, and long-term use is well tolerated. It is included in oral contraceptives to mitigate the effects of 'estrogen-only' therapy. Ethinyl estradiol is a synthetic estrogen whose toxicity has been thoroughly investigated in vitro and in vivo across many species. With few exceptions, animal models have accurately predicted toxicity in humans. Currently, enough clinical and epidemiological data on long-term human use of estrogens and progesterones are available that there is no longer a benefit to carrying out nonclinical testing for variations in the dose regimens of these compounds.

One new item in this amendment was a toxicology assessment carried out by the sponsor for leachable impurities originating from the product packaging. The impurities were [redacted]. We concurred with the sponsor's analysis that leachable impurities in this product do not reach levels that are of toxicological significance. b(4)

B. Pharmacologic activity

Levonorgestrel and ethinyl estradiol are synthetic analogs of progesterone and estradiol that have pharmacological actions consistent with their chemical class. Levonorgestrel targets the progesterone receptor (A and B isoforms), which are expressed in tissues of the

reproductive tract, breast, and central nervous system (CNS). Ethinyl estradiol targets the estrogen receptor (α and β isoforms), which are also distributed throughout the reproductive system and CNS. Levonorgestrel and ethinyl estradiol have multiple physiological effects, and regulate fertility (suppression of ovulation), development, metabolism, and behavior.

C. Nonclinical safety issues relevant to clinical use

There are no new nonclinical safety issues relevant to clinical use.

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/s/

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-864**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**May 27, 2005, original submission**
	August 22, 2006, resubmission
PRODUCT:	**Levonorgestrel (90 µg) /**
	Ethinyl Estradiol (20 µg) Continuous Use
INTENDED CLINICAL POPULATION:	**For contraceptive use in women**
SPONSOR:	**Wyeth Pharmaceuticals**
DOCUMENTS REVIEWED (original submission):	**Module 2: Common Technical Document Summaries. 2.4 Nonclinical Overview**
REVIEW DIVISION:	**Division of Reproductive and Urologic Products (HFD-580)**
PHARM/TOX REVIEWER:	**Leslie McKinney, Ph.D.**
PHARM/TOX SUPERVISOR:	**Lynnda Reid, Ph.D.**
DIVISION DIRECTOR (Acting):	**Scott Monroe, M.D.**
PROJECT MANAGER:	**John Kim, R.Ph., J.D.**

Date of review submission to Division File System (DFS): November 17, 2006

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

This resubmission constitutes a complete response to the Approvable letter issued by the Division on June 27, 2006. There are no new nonclinical issues for the resubmission. Based on previously submitted nonclinical data for levonorgestrel (LNG) and ethinyl estradiol (EE), we recommend approval of the LNG 90 μg/EE 20 μg dosage in the continuous use regimen.

B. Recommendation for nonclinical studies

At a guidance meeting held April 8, 2002, DRUP indicated to Wyeth that nonclinical studies performed to support marketed LNG/EE products were sufficient to support the proposed continuous use regimen. Therefore, no new nonclinical studies were carried out in support of the original submission or for the resubmission.

C. Recommendations on labeling

There are no Pharm/Tox recommendations for changes in the proposed labeling for LNG/EE combination oral contraceptives.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

There were no new nonclinical studies submitted in support of this application. Levonorgestrel is a 'third generation' synthetic progestin that has been widely used in many types of oral contraceptives. Its toxicological profile is well understood across species, and long-term use is well tolerated. It is included in oral contraceptives to mitigate the effects of 'estrogen-only' therapy. Ethinyl estradiol is a synthetic estrogen whose toxicity has been thoroughly investigated in vitro and in vivo across many species. With few exceptions, animal models have accurately predicted toxicity in humans. Currently, enough clinical and epidemiological data on long-term human use of estrogens and progesterones are available that there is no longer a benefit to carrying out nonclinical testing for variations in the dose regimens of these compounds.

B. Pharmacologic activity

Levonorgestrel and ethinyl estradiol are synthetic analogs of progesterone and estradiol that have pharmacological actions consistent with their chemical class. Levonorgestrel targets the progesterone receptor (A and B isoforms), which are expressed in tissues of the reproductive tract, breast, and central nervous system (CNS). Ethinyl estradiol targets the estrogen receptor (α and β isoforms), which are also distributed throughout the reproductive system and CNS. Levonorgestrel and ethinyl estradiol have multiple physiological effects, and regulate fertility (suppression of ovulation), development, metabolism, and behavior.

C. Nonclinical safety issues relevant to clinical use

There are no new nonclinical safety issues relevant to clinical use.

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/s/

Leslie McKinney
11/20/2006 01:32:01 PM
PHARMACOLOGIST

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PHARMACOLOGIST

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-864**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**5/27/05**
PRODUCT:	**Levonorgestrel (LNG) (90 µg) / Ethinyl Estradiol (EE) (20 µg) Continuous Use**
INTENDED CLINICAL POPULATION:	**For contraceptive use in women**
SPONSOR:	**Wyeth Pharmaceuticals**
DOCUMENTS REVIEWED:	**Module 2: Common Technical Document Summaries. 2.4 Nonclinical Overview**
REVIEW DIVISION:	**Division of Reproductive and Urologic Products (HFD-580)**
PHARM/TOX REVIEWER:	**Leslie McKinney, Ph.D.**
PHARM/TOX SUPERVISOR:	**Lynnda Reid, Ph.D.**
DIVISION DIRECTOR:	**Daniel Shames, M.D. F.A.C.S.**
PROJECT MANAGER:	**John Kim, R.Ph., J.D.**

Date of review submission to Division File System (DFS): 2/9/06

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

NDA 21-864 Levonorgestrel (LNG)(90 ug) / Ethinyl Estradiol (EE) (20 ug) Continuous Use has been submitted by Wyeth Pharmaceuticals for contraception. LNG/EE combination pills have been previously marketed by Wyeth for this indication at comparable or higher doses using monthly regimens, but have not yet been approved for continuous use. There are no new non-clinical issues for the proposed lower dosage. Based on previously submitted Pharm/Tox data for LNG ad EE, we recommend approval of the LNG 90 ug/EE 20 ug dosage in the continuous use regimen.

B. Recommendation for nonclinical studies

At a guidance meeting held April 8, 2002, DRUP indicated to Wyeth that preclinical pharm/tox studies performed to support marketed LNG/EE products were sufficient to support the proposed continuous use regimen. Therefore, no new pharm/tox studies were carried out in support of this submission.

C. Recommendations on labeling

There are no pharm/tox recommendations for changes in the proposed labeling for LNG/EE combination oral contraceptives.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

There were no new nonclinical studies submitted in support of this application.

B. Pharmacologic activity

Effects on target tissues are not expected to be different from the approved dosages.

C. Nonclinical safety issues relevant to clinical use

There are no new nonclinical safety issues relevant to clinical use.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

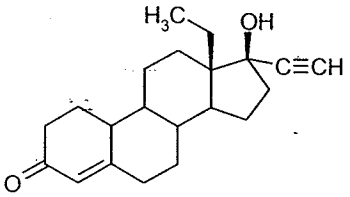
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-864
Review number: 1
Sequence number/date/type of submission: 000 / 5-27-2005 / original
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Wyeth Pharmaceuticals
Manufacturer for drug substance: Levonorgestrel: Schering AG
Ethinyl Estradiol: Schering AG
Reviewer name: Leslie McKinney, Ph.D.
Division name: Division of Reproductive and Urologic Products
HFD #: 580
Review completion date: 1/31/06

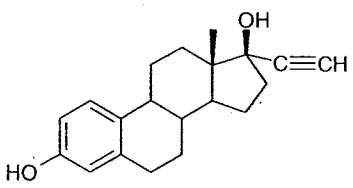
Drug:

Trade name: Levonorgestrel (LNG) / Ethinyl Estradiol (EE)
Generic name: none
Code name: Levonorgestrel: WY-5104 / Ethinyl Estradiol: AY-3877
Chemical name:
LNG: (17α)-(–)-13-ethyl-17-hydroxy-18,19-dinorpregn-4-en-20-yn-3-one
EE: (17α)-19-norpregna-1,3,5)10)-trien-20-yne-3,17-diol
CAS registry number:
Levonorgestrel: 797-63-7
Ethinyl Estradiol: 57-63-6
Molecular formula/molecular weight:
Levonorgestrel: $C_{21}H_{28}O_2$ / 312.45
Ethinyl Estradiol: $C_{20}H_{24}O_2$ / 296.4

Structure:



Levonorgestrel



Ethinyl Estradiol

Relevant INDs/NDAs/DMFs: NDAs of currently marketed LNG/EE products:

Application #	Approval Date	Brand Name	Dosage (ug)	HED ug/m^2	Regimen
NDA 20-860	1998	Levlite®	LNG 100/EE 20	61.7/12.3	21 of 28 d
NDA 20-683	1997	Alesse™	LNG 100/EE 20	61.7/12.3	21 of 28 d
ANDA 73-594	1993	Levora®	LNG 150/EE 30	92.5/18.5	21 of 28 d
NDA 19-190	1984	Triphasil®-28	LNG 50/EE 30 LNG 75/EE 40 LNG 125/EE 30	30.8/18.5 46.25/24.7 77.1/24.7	d 1-6 d 7-11 d 12-21
NDA 18-782	1982	Nordette®-28	LNG 150/EE 30	92.5/18.5	21 of 28 d
NDA 17-802	1976	Lo/Ovral®-28	LNG 300/EE 30	185/18.5	21 of 28 d

Drug class: steroid hormones

Intended clinical population: For contraceptive use in women

Clinical formulation:

Sponsor's Table (some formula notes omitted by the reviewer)

Ingredient	Reference to Standards	Function	Unit Dose (mg/tablet)
Tablet core			
Active Ingredients:			
Levonorgestrel, (micronized)[a]	USP	Active	0.090
Ethinyl Estradiol (micronized)[a]	USP	Active	0.020
Other Ingredients:			
Microcrystalline Cellulose	NF		
Lactose Monohydrate[a]	NF		
Magnesium Stearate	NF		
Polacrilin Potassium	NF		
Polyethylene Glycol	NF		
	USP		
Montanic Ester Wax	DAB10[e]		
Total Weight (Coated Tablets)			70.5

b(4)

a. The amount of each drug substance is adjusted against the lactose content.
e. DAB 10 = Deutsches Arzneibuch (German Pharmacopoeia, 10th Edition)

Route of administration: oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance : NDA 21-864 is being filed as a 505 (b)(1) application. All non-clinical data were derived from studies conducted by Wyeth for previous IND or NDA filings. For informational purposes, some data from published reports have also been included.

Studies reviewed within this submission: There were no new non-clinical studies submitted for review.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

LNG, a member of the norethindrone family of progestins, and EE, a derivative of natural estrogen, are among the most widely used active ingredients in oral contraceptives. EE has been a component of oral contraceptives from the earliest formulations. LNG is a member of the second generation of oral contraceptives, defined as products containing levonorgestrel or other members of the norethindrone family and 30 or 35 ug of EE. LNG is among the most potent of the synthetic progestins and mimics the pharmacological properties of progesterone. Ethinyl estradiol binds to the estrogen receptor and affects the same target tissues as estrogen: ovary, uterus, vagina, cervix, pituitary, and bone. Each contributes to the inhibition of ovulation.

2.6.2.2 Primary pharmacodynamics

Mechanism of action:

LNG and EE bind to the progesterone and estrogen receptors, respectively, in target tissues of the reproductive tract, breast, bone, and pituitary.

Drug activity related to proposed indication:

LNG contributes to the prevention of ovulation primarily by suppressing luteinizing hormone (LH) secretion. EE suppresses follicle-stimulating hormone (FSH) secretion and thus prevents the maturation of an ovulatory follicle.

2.6.2.3 Secondary pharmacodynamics

LNG has weak relative affinity for the androgen receptor (20% that of 5α-dihydrotestosterone).

2.6.2.4 Safety pharmacology

LNG/EE combination oral contraceptives have acceptable safety profiles in animals and humans. There is very little acute toxicity, other than nausea, which can occur at higher doses of estrogen. Other toxicities associated with oral contraceptive use, such as thrombosis, changes in liver metabolism, and carcinogenicity, appear with longer-term use.

2.6.2.5 Pharmacodynamic drug interactions

Because LNG and EE are extensively metabolized in the liver, liver disease could affect efficacy, oral contraceptives are not known to specifically aggravate cirrhosis or previous hepatitis. Estrogen inhibits bile formation, so acute or chronic cholestatic liver disease is a contraindication for use.

2.6.3 PHARMACOLOGY TABULATED SUMMARY N/A

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Orally administered LNG and EE are rapidly absorbed, circulate in protein-bound form, and undergo significant first pass metabolism in the liver. Both LNG and EE are excreted rapidly, primarily in metabolized form, which necessitates readministration on a daily basis.

2.6.4.2 Methods of Analysis N/A

2.6.4.3 Absorption

LNG: Absorption of LNG following oral administration is rapid (Cmax observed at 1-2 h) in all species examined except for rhesus monkeys, which has delayed absorption (Cmax observed at 9 h). Oral availability is highest in humans (100%) and lowest in Rhesus monkeys (9%). LNG was cleared very rapidly in dogs ($T_{1/2}$ = 1.4 h) and more slowly in mice, rats, and Rhesus monkeys ($T_{1/2}$ range = 6.7-23.1 h).

EE: Oral bioavailability of EE in animal species is very low (ranging from <1% in monkeys to 9% in beagle dogs), due to rapid hepatic extraction of the drug. In humans, the first-pass effect is not as pronounced, and bioavailability is higher (60%). Steady state $T_{1/2}$ of EE is 18 h.

2.6.4.4 Distribution

Distribution of ^{14}C-LNG and ^{3}H-EE was measured following administered of a single oral dose in rats. ^{14}C was widely distributed in ~1 hr, with highest concentration in the GI tract and liver. Tissues were essentially cleared of ^{14}C at 96 h. Very similar findings were obtained for ^{3}H-EE. Distribution to fetuses and to milk was also investigated in the rat following single oral dosing at gestation day (GD) 17. Both ^{14}C-LNG and ^{3}H-EE were lower in the fetus than in maternal blood. ^{14}C-LNG was elevated in milk compared to plasma but ^{3}H-EE was not.

Preferential distribution of LNG to the liver was further illustrated in a rabbit study. In the rabbit, maximum concentration of ^{3}H-LNG was highest in bile, appearing at 3-4 orders of magnitude higher concentration than in kidney, vagina, and myometrium. Tissues were essentially cleared by 24 h post-dosing.

LNG is almost completely bound (>99%) to serum proteins in humans. It is thought to be bound with high affinity to a pool of sex hormone binding globulin (SHBG) and more weakly bound to serum albumin. EE is also bound to serum albumin (97%) and can induce an increase in serum SHBG. ^{14}C-LNG and ^{3}H-EE can therefore affect circulating levels of bound/free of each other.

The sponsor referred to existing pharmacokinetic data on the combination product LNG 100 ug/EE 20 ug as being most relevant for evaluating the likely distribution of the currently proposed lower dose form. For LNG, bioavailability is 100% and steady state plasma concentrations, achieved by day 11, range from 1.9 to 6.0 ng/mL. It is primarily bound to SHBG, and is metabolized via reduction and hydroxylation, followed by conjugation, with a $T_{1/2}$ at steady state of 36 h. In humans, LNG and its metabolites are excreted to a greater extent in urine than in feces.

For EE, bioavailability is less than for LNG, ranging from 40-60%. Steady state is reached by day 6, and plasma concentrations range from 10.5 – 77 pg/mL. SHBG binds 97% of EE, and further induced by EE. EE can be metabolized in the gut presystemically, where it can undergo conjugation. In the liver, it is hydroxylated by cytochrome P450, followed by conjugation. It is excreted with a $T_{1/2}$ of 18 h, primarily in urine and feces.

2.6.4.5 Metabolism

Metabolites of LNG have been characterized in humans, primates, and rodents. In humans, following reduction of the A ring and hydroxylation, metabolites are conjugated to sulfates or glucuronides for secretion. Sulfates circulate in plasma and glucuronides are found in urine. The sites of catalysis were not identified.

EE also undergoes hydroxylation and conjugation. The sponsor identified CYP3A4 as the primary oxidative enzyme, with CYP2C, CYP2E, and CYP3A, but not CYP2D6, also involved. It was noted that EE, but not LNG, retard the elimination of caffeine and metamizol metabolites, indicating an interaction with methylcholanthrene and phenobarbital inducible isozymes.

2.6.4.6 Excretion

In rat, rabbit, monkey, baboon, and human, excretion of LNG is primarily through urine and feces (total amount recovered: 78-96.8%). In humans, 86.4% of a 1.5 mg oral dose was excreted, virtually all in metabolized form.

For EE, in keeping with the extensive hepatic metabolism of this drug, nearly all (~80%) of the excretion in rat and dog was via feces. Exact percentages were not given for primates or humans.

2.6.4.7 Pharmacokinetic drug interactions

The sponsor indicated that there was no effect on LNG pharmacokinetics when 17β-estradiol was co-administered with LNG iv in dogs. Pharmacokinetic interactions are possible between oral contraceptives and other drugs that affect the metabolism of contraceptive steroids (see Alesse™ label for examples). It has also been reported that progestins, including LNG, have P-glycoprotein inhibitory activity, which means that clearance of other drugs through P-glycoprotein activity could be reduced.

2.6.4.8 Other Pharmacokinetic Studies N/A

2.6.4.9 Discussion and Conclusions

The ADME characteristics of LNG and EE are well understood and should be unaffected by the proposed reduction of EE dose. Combination LNG/EE pills are already used in a chronic dose regimen; administration in a continuous use regimen is unlikely to produce any metabolic changes that have not already been noted.

2.6.4.10 Tables and figures to include comparative TK summary N/A

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

The sponsor submitted ADME data for LNG and EE alone and in combination in summary form. Tables were provided listing individual studies that were carried out by Wyeth or were referenced to open literature. The table below lists the ADME studies carried out for the LNG/EE combination.

Overview of Drug Metabolism Studies with LNG/EE

Type of Study	Test Systems	Test Article	Method of Administration	Dosage/Analyte	Citation
Absorption					
Single-dose	rat	LNG/EE	oral	375/200 ug/kg	Tsukamoto et al., 1992a
Repeat-dose	rat	LNG/EE	oral	375/200 ug/kg	Tsukamoto et al., 1992b
Distribution					
Single-dose	rat	LNG/EE	oral	375/200 ug/kg	Tsukamoto et al., 1992a
Repeat-dose	rat	LNG/EE	oral	375/200 ug/kg	Tsukamoto et al., 1992c
Repeat-dose	rat	LNG/EE	oral	375/200 ug/kg	Tsukamoto et al., 1992a

Excerpted from sponsor's Table 7.0-1 located in Module 2. CTD Summaries. 2.4. Nonclinical Overview, p 30.

In addition to the above studies on the ADME of LNG and EE in combination, the sponsor summarized a number of studies assessing the ADME of LNG and EE alone. LNG was evaluated in 43 separate studies in mice, rats, rabbits, dogs, Rhesus monkeys, baboons, and African green monkeys, as well as in in vitro preparations of rat liver microsomes. These studies dated from the 1970's and included oral, iv, and sc routes of administration. EE was evaluated in 10 studies conducted in rats, dogs, rabbits, baboons, and Rhesus monkeys by oral and iv routes of administration, and in in vitro preparations.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

Toxicology of steroid hormones alone and in combination has been extensively studied in several rodent species, dogs, and monkeys, where both acute and chronic toxicity has been found to be low. The most relevant animal model for predicting human responses is the monkey. Both rat and dog are considered to be more sensitive to the effects of steroid hormones in both general and specific ways, and toxicological studies conducted in these species are therefore interpreted conservatively.

It is generally accepted that acute toxicity of estrogens or progesterones administered separately in rodents is caused by liver and kidney failure. In repeat-dose studies, cholestasis is a predominant finding, primarily due to impaired bile formation. A NOEL has been reported for EE-induced cholestasis in rats of 0.25 mg/kg/day (1.5 mg/m^2). In dogs, hematopoietic effects are prominent. Depressed erythropoietic activity and thrombocytopenia are among the findings. The NOEL reported for EE-induced hematotoxicity in dogs is between 0.04 and 0.2 mg/kg/day (0.8 – 4 mg/m^2).

A 10-year monkey study carried out by the sponsor showed that long-term systemic toxicity of LNG is low. Other long-term studies in monkeys using other estrogens and progestins did not result in significant toxic effects.

In humans, it is well known that there is a dose-dependent increase in the risk of thrombosis related to the use of estrogen. Estrogen increases the production of clotting factors, including factor V, factor VIII, factor X, and fibrinogen. Liver metabolism is also affected by both estrogens and progestins. At low doses, however, total cholesterol and triglycerides do not show large changes, although the ratio of HDL to LDL may be affected. However, as summarized by the sponsor, no unique toxicities are associated with the LNG/EE combination at the dosages proposed in this NDA.

Genetic toxicology:

The genotoxicity of LNG and EE in combination has not been studied, but each has been evaluated separately. Neither LNG nor EE are considered mutagenic. Assays that evaluate non-mutational genotoxicity have yielded mixed results for both LNG and EE. Because genotoxicity assays are carried out using very high doses of LNG and EE, it is generally concluded that LNG and EE are unlikely to have significant genotoxicity at the doses used in oral contraceptives.

Carcinogenicity:

Long-term studies in monkeys, and large epidemiological studies in women, have established the carcinogenic risk associated with chronic use of combined oral contraceptives. The continuous use regimen proposed in this NDA is unlikely to yield any changes in the risk profile.

Reproductive toxicology:

In rat, the effects of LNG and EE on fertility were consistent with the contraceptive properties of the hormones. Developmentally, while embryofetal effect can be induced if the combination was taken during pregnancy, neither LNG nor EE, alone or in combination are considered to be teratogenic. Current labeling of LNG/EE oral contraceptives is Pregnancy Category X.

2.6.6.2 Single-dose toxicity

Acute single-dose toxicity of LNG/EE in combination in mice is >5000 mg/kg, which is ~6 orders of magnitude greater than the proposed human equivalent dose. Rats showed similar sensitivity. This value held for ratios of LNG:EE of 5:1, 5:3, 15:8, and 25:6.

2.6.6.3 Repeat-dose toxicity

Only one repeat-dose (28 day) study was cited for LNG/EE in combination, which was carried out in female rats by oral gavage in 1990. All other repeat dose studies cited by the sponsor were for LNG or EE administered separately.

Findings in rats that were exposed to LNG:EE at a 5:3 ratio at doses ranging from 0.00032 to 40 mg/kg/day included: estrous cycle changes, vaginal alterations (not specified), ovarian atrophy, hepatic steatosis, atrophy of gonadotropin-releasing cells in the pituitary, decreased osteoclasts and osteoblasts in sternum and femur, and atrophy of the spleen, thymus, and mesenteric lymph nodes. Hematology changes listed by the sponsor were: decreased RBC, hematocrit, hemoglobin, and lymphocytes. Reticulocytes and neutrophils were increased, and

platelets and prothrombin times increased. Clinical chemistry changes showed decreased total cholesterol, increased alkaline phosphatase and alanine aminotransferase, total protein, and albumin. It was noted that the hepatic and hematopoietic changes were observed only at the highest dose of 40 mg/kg/day (25 mg LNG/15 mg EE).

Although the literature on LNG:EE in combination is small, other studies have been conducted using other combinations of estrogens and progesterone for long durations at high doses that did not yield significant systemic toxicity, including primates.

Repeat dose studies of LNG alone have been previously carried out in rat (1 yr oral gavage) and dog (6 month oral gavage). An extremely long duration study (7 years) was also carried out dog, using a 21 day on, 7 day off dosing cycle. Dosing in the rat study was up to 25 mg/kg/day (150 mg/m^2), and caused decreased uterine and pituitary weight, increased liver:body wt ratio, and decreased total cholesterol. Dog studies used a high dose of only 0.5 mg/kg/day (10 mg/m^2), which is still ~2 orders of magnitude higher than the proposed human dosage. Effects in dogs included inhibition of estrus and ovulation, clitoral reddening and enlargement, and decreased RBC parameters. Mammary enlargement and increased incidence of mammary gland nodules (with one finding of adenocarcinoma) were found in the 6 month and 7 year studies, respectively, and may be a unique finding in the dog. Liver-related findings included decreased total cholesterol, and increased ALT. Increased fibrinogen was noted in the 7 year study.

Repeat-dose primate studies using LNG alone were conducted in cynomolgous and rhesus monkeys. Dosages up to 2.5 mg/kg (30 mg/m^2) were orally administered for 3 months or 1 year, and one 10 year study was conducted using a regimen of 1 mg/kg/day for 21 days followed by 7 day without treatment. In the two shorter term studies, findings included increased body weight, and decreased serum cholesterol and phospholipids. Endometrial and pancreatic cell hyperplasia was noted in the 3 month study, and suppression of ovarian follicle development in the 1 year study. The 10 year study findings were similar, and included ovarian and uterine atrophy and macular granulation. Elevation of glutamic oxaloacetic transaminase (GOT) was not accompanied by microscopic liver changes. Findings in monkeys were reversible.

Repeat dose studies of EE alone that were conducted in rat and dog yielded findings of exaggerated pharmacological effects on reproductive organs, including uterine hypertrophy, vaginal keratinization, mammary gland development, and ovarian and testicular atrophy. In rat, liver findings were reported that included hepatocellular hyperplasia (1-10 mg/kg/day), and in dog, 1 year exposures to 0.5 or 1 mg/kg/day produced mortality and moribundity. There were significant hematological effects in dog, including anemia, leukopenia, and thrombocytopenia that were observable at lower doses as well (down to 0.2 mg/kg/day). Further lowering of the dose to 0.04 mg/kg/day eliminated the hematological effects.

2.6.6.4 Genetic toxicology

Genotoxicity studies have not been performed on the LNG/EE combination product. However, they have each been extensively tested individually. By the standard battery of mutation assays, neither LNG nor EE have been found to be mutagenic. Assays that evaluate non-mutational genotoxicity (sister chromatid exchange, unscheduled DNA synthesis, DNA strand breaks and DNA adducts) have yielded mixed results for both LNG and EE, but the relevance of these findings to human carcinogenicity is uncertain.

2.6.6.5 Carcinogenicity

It is generally recognized that long-term, high-dose use of some estrogens and progesterones can lead to tumor formation in sensitive tissues in some rodent species and dog. However, for various reasons, data from these animal models are not considered to be highly relevant to humans. Data from long-term studies in monkeys, which is the more relevant species, showed minimal tumor incidence in animals that were treated with EE and norethindrone acetate.

Large epidemiological studies in women remain the best measure of the potential carcinogenicity of combined estrogen/progesterone oral contraceptives. There is a recognized increased risk of breast and cervical cancer, but a decreased risk of ovarian and endometrial cancer. Because oral contraceptive use occurs chronically over many years, initiation of a continuous use regiment is not likely to significantly alter the carcinogenicity profile of these hormones.

2.6.6.6 Reproductive and developmental toxicology

A series of reproductive/developmental studies were carried out in rat and rabbit that evaluated the effect of orally administered (by gavage) LNG/EE at various doses in a 5:3 ratio. The regimens were (as listed by the sponsor):

- Effects on female fertility and offspring growth, development and reproductive functioning of offspring after daily treatment of females for 14 days prior to mating.
- Effects of female fertility and offspring growth, development and reproductive functioning of offspring after daily treatment of females for 14 days prior to mating and during the cohabitation period with males.
- Effects on embryo implantation and development after daily treatment of females on days 0 through 7 of gestation (day 0 being the day of mating)
- Effects on morphological development of fetuses exposed in utero on days 7 through 17 of gestation
- Effects on parturition, preweaning mortality, growth, development, and reproductive functioning of offspring after daily treatment of mated females on gestation day 17 through postnatal day 20 or 24
- Effects on milk production after treatment of females on postnatal days 0 through 14
- Effects on morphological development of rabbit fetuses exposed in utero on days 6 through 18 of gestation

Male reproductive performance was not assessed.

The following results were observed:

- Increased female copulatory interval
- decreased number of implantation sites
- increases in pre- and post-implantation losses
- decreased numbers of offspring and offspring body weights
- transient delayed development of pups
- increased air righting reflex time and memory impairment in pups
- precocious vaginal opening
- reduced anogenital distance (males) in pups
- reduced milk production.

There were no malformations in either rat or rabbit fetuses after exposure in utero. LNG alone, when applied late in pregnancy (GD 17 to GD 20) resulted in masculinization of female fetuses.

2.6.6.7 Local tolerance: N/A

2.6.6.8 Special toxicology studies: N/A

2.6.6.9 Discussion and Conclusions

There are no new toxicological concerns for the proposed new dose and continuous use regimen for LNG/EE.

2.6.6.10 Tables and Figures: N/A

2.6.7 TOXICOLOGY TABULATED SUMMARY

The sponsor submitted toxicology data for LNG and EE alone and in combination in summary form. Tables were provided listing individual studies that were carried out by Wyeth or were described in the open literature. The table below lists the toxicology studies carried out for the LNG/EE combination.

Single- and Repeat-Dose Toxicity Studies with Levonorgestrel/Ethinyl Estradiol

Type of Study	Species and Strain	Method of Administration	N/Sex/ Group	Duration of Dosing	Dosage (mg/kg/day)	Report #
Single-dose	Mice CD-1	Oral	5	1 day	5000 mg/kg LNG:EE=5:1	Wyeth-Ayerst GTR-14765
					5000 mg/kg LNG:EE=5:3	Wyeth-Ayerst GTR-14767
					5000 mg/kg LNG:EE=15:8	Wyeth-Ayerst GTR-14769
					5000 mg/kg LNG:EE=25:6	Wyeth-Ayerst GTR-14771
Single-dose	Rats CD	Oral	5	1 day	5000 mg/kg LNG:EE=5:1	Wyeth-Ayerst GTR-14404
					2000, 5000 mg/kg LNG:EE=5:3	Wyeth-Ayerst GTR-14766
					5000 mg/kg LNG:EE=15:8	Wyeth-Ayerst GTR-14768
					5000 mg/kg LNG:EE=25:6	Wyeth-Ayerst GTR-14770
Repeat-dose	Rat SD	Oral gavage	20F 10F 20F	1 month	0, 0.00032 or 0.016 0.8 or 40 LNG:EE=5:3	Wyeth-Ayerst GTR-18398

Excerpted from sponsor's Table 7.0-2 located in Module 2. CTD Summaries. 2.4. Nonclinical Overview, p 38.

In addition to the above studies on the toxicology of LNG and EE in combination, the sponsor summarized a number of studies assessing the toxicology of LNG and EE alone. LNG was evaluated in 6 separate repeat-dose studies in rat, dog, Cynomolgus and Rhesus monkeys. These studies dated from the 1970's and included oral routes of administration (capsule, gavage, and dietary). General toxicity of EE alone was not further evaluated.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

From a Pharm/Tox perspective, there are no new safety concerns for approval of Levonorgestrel (LNG) (90 ug) / Ethinyl Estradiol (EE) (20 ug) Continuous Use. Contraindications for and complications following use of combined oral contraceptives are detailed in the current labeling and should be applied to use of the new dosage in the continuous use regimen.

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/s/

Leslie McKinney
2/9/2006 05:38:06 PM
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Lynnda Reid
2/13/2006 03:27:34 PM
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45 Day NDA Meeting Checklist
Pharmacology/Toxicology

NDA Number: 21-864 **Date: 12-July-2005**
Drug Name: Levonorgestryl/ethinyl estradiol **Reviewer:** Leslie McKinney Leonard
Sponsor: Wyeth

Date CDER Received: May 27, 2005
Filing Date: July 12, 2005
User Fee Date: March 26, 2006
Expected Date of Draft Review: December

On initial overview of the Pharm/Tox portion of the NDA application

1)	On its face, is the Pharm/Tox section of the NDA organized in a manner to allow substantive review to begin?	yes	
2)	Is the Pharm/Tox section of the NDA indexed and paginated in a manner to allow substantive review to begin?	yes	
3)	On its face, is the Pharm/Tox section of the NDA legible so that substantive review can being? Has the data been presented in an appropriate manner?	yes	The pharm/tox data in support of this submission is presented in the form of previously published studies on levonorgestrel and ethinyl estradiol. Literature references have been submitted in full.
4)	Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA?	yes	At a guidance meeting held April 8, 2002, DRUDP indicated to Wyeth that preclinical pharm/tox studies performed to support marketed LNG/EE products are sufficient to support the proposed continuous-use program. Therefore, no new pharm/tox studies were carried out in support of this submission.
5)	If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the Sponsor clearly defined the differences and submitted reviewable supportive data?	yes	The formulation to be marketed is a lower dose formulation of levonorgestrel. A continuous dosing regimen is proposed.
6)	Does the route of administration used in animal studies appear to be the same as the intended human exposure? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	yes	

7)	Has the sponsor submitted a statement(s) that all the pivotal Pharm/Tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	yes	Sponsor cites extensive literature and studies conducted under previous INDs and NDAs in support of this application.
8)	Has the sponsor submitted a statement(s) that the Pharm/Tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?	yes	See previous statement.
9)	Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.57? Is information available to express human dose multiples in either mg/m^2 or comparative serum/plasma AUC levels?	yes yes yes	
10)	From a Pharm/Tox perspective, is this NDA fileable? If not, please state in item #11 below why it is not.	yes	
11)	Reasons for refusal to file:		

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/s/

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7/12/05 04:14:27 PM
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