CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 20-946

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				X
Approvable Letter			X	
Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI			X	
Pharmacology Review(s)			X	
Statistical Review(s)			X	
Microbiology Review(s)			X	
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)			X	
Administrative Document(s)	X			
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20-946

Trade Name: Preven Emergency Conctraceptive Kit

Generic Name:(levonorgestrel ethinyl estradiol tablets and pregnancy test)

Sponsor: Gynetics, Inc.

Approval Date: September 1, 1998

Indication:Provides for the use of Preven Emergency Contraceptive Kit (levonorgestrel and ethinyl estradiol tablets and pregnancy test) for prevention of pregnancy

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20-946

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-946

SEP 01 1998

Gynetics Inc.
Attention: Ms. Margaret P. Filipiak
Regulatory Manager
56 Locust Lane
Princeton, NJ 08540

Dear Ms. Filipiak:

Please refer to your new drug application (NDA) dated November 26, 1997, received December 1, 1997, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Preven™ Emergency Contraceptive Kit (levonorgestrel and ethinyl estradiol tablets and pregnancy test).

We acknowledge receipt of your submissions dated December 5, 1997; February 9, March 10 and 25 (2), April 2, 23 and 27, May 6, 15, and 20, June 8 and 16, July 17, August 6, 11, 13, 20, 21 (telefacsimile), 25, 29 and 31 (telefacsimile) and September 1, (telefacsimile) 1998. Your submission of April 27, 1998, extended the user fee goal date for this application to September 1, 1998.

This new drug application provides for the use of Preven™ Emergency Contraceptive Kit (levonorgestrel and ethinyl estradiol tablets and pregnancy test) for prevention of pregnancy.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

From a chemistry, manufacturing and controls perspective, an 18-month expiration date for the product is acceptable based on additional stability data provided. However, you are reminded that this 18-month period is from the date of manufacture of the tablets and includes the storage time in the bulk containers.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package and patient package inserts submitted September 1, 1998, immediate container label submitted August 31, 1998 and outer carton label submitted September 1, 1998). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-946." Approval of this submission by FDA is not required before the labeling is used.

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

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

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

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

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

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

Sincerely,

/S/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-946

MEDICAL REVIEW(S)

SEP 01 1998

NDA 20-946
Submission Date: September 01, 1998

Medical Officer's Final Review of Label
Preven™Emergency Contraceptive Kit
Four Levonorgestrel-0.25mg/Ethinyl Estradiol-0.05mg Tablets
Amendment #
Gynétics, Inc., Princeton, NJ 08540

Reviewer's Comment:

After several internal meetings with the Deputy Division Director and numerous teleconference discussions with the Sponsor, the following revisions were made to the August 7, 1998, label (review). The final Draft Label as submitted 9/1/98 (with incorporated changes) is now agreeable to both the Reviewer and the Sponsor.

/S/

Shelley R. Slaughter, MD, PhD. 9/1/98
Medical Officer

cc:
NDA 20-946
HFD-580/ L. Rarick/ M. Mann/ S. Slaughter/ C. Kish

I concur MM MD 9/1/98

AUG 2 2 1998

August 27, 1998
Medical Officer's Review
NDA 20-946
Preven™ Emergency Contraceptive Kit
4Levonorgestrel-0.25mg/Ethinyl Estradiol-0.05 mg Tablets
Draft Label
Amendment #015-8/19/98
Gynétics, Inc., Princeton, NJ 08540

Reviewer Comments: This is the review of the 8/19/98 Draft Label from Gynétics (Response labeling to FDA). This review incorporates the changes submitted by Gynétics which with we are in agreement. We strongly advise that the Sponsor remove the references from the Prescribing Information section of the Label. This suggestion follows the format of the revised Labeling Guidance for Combined Oral Contraceptives which is now in the final stages of Draft and will be implemented soon.

/S/

Shelley R. Slaughter, MD, Ph.D. 8/27/98
Medical Officer

cc:
NDA 20-946
HFD-580/L. Rarick/M. Mann/ S. Slaughter/ C.Kish

I concur - M Mann MD. 8/27/98

Kish

AUG 10 1998

August 7, 1998
Medical Officer's Review
NDA 20-946
Preven™ Emergency Contraceptive Kit
4 Levonorgestrel-0.25mg/Ethinyl Estradiol-0.05mg Tablets
Draft Label
Draft 17:3/30/98-Amendment #005-4/~~4~~/98
Gynetics, Inc., Princeton, NJ 08540

/S/

Shelley R. Slaughter, MD, Ph.D.
Medical Officer

8/7/98

I concur

8/10/98

cc:
NDA 20-946
HFD-580/L. Rarick/ M. Mann/ S. Slaughter/ C. Kish

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-946

CHEMISTRY REVIEW(S)

Kish

AUG 28 1998

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

NDA: 20-946
CHEMISTRY REVIEW # 2 **DATE REVIEWED:** 25 Aug 1998

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	26 Nov. 1997	1 Dec. 1997	4 Dec. 1997
AMENDMENTS	9 Feb. 1998	10 Feb. 1998	
	25 Mar. 1998	27 Mar. 1998	
	15 May 1998	18 May 1998	
	20 May 1998	21 May 1998	
	17 July 1998	20 July 1998	
	11 Aug 1998	12 Aug 1998	
	20 and 21 Aug 1998		

NAME & ADDRESS OF APPLICANT: Gynetics Inc.
198, Route 206, Somerville, NJ 08876

DRUG PRODUCT NAME

Proprietary:	Preven Emergency Contraceptive Kit
Nonproprietary/Established/USAN:	Levonorgestrel and Ethinyl Estradiol Tablets, USP
Code Name/#:	
Chem.Type/Ther.Class:	3P

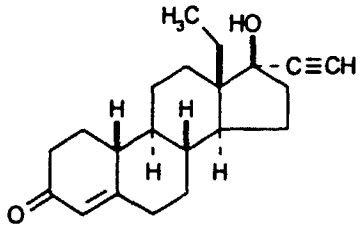
ANDA Suitability Petition / DESI / Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION: Progetin/Estrogen for emergency postcoital contraception.

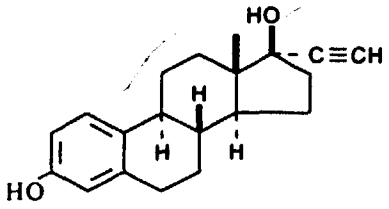
DOSAGE FORM:	Tablets
STRENGTHS:	0.25 mg Levonorgestrel/ 0.05 mg Ethinyl Estradiol
ROUTE OF ADMINISTRATION:	oral
DISPENSED:	X Rx __ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Molecular Formula: Levonorgestrel: $C_{21}H_{28}O_2$; Ethinyl Estradiol: $C_{20}H_{24}O_2$
Molecular Weight: Levonorgestrel : 312.5; Ethinyl Estradiol: 296.41
Chemical Name: Levonorgestrel: 18, 19-Dinorpregn-4-en-20-yn-3-one, 13-Ethyl-17-hydroxy-, (17α)-(-)
Ethinyl Estradiol: 19- Norpregn-1,3,5 (10) -triene-20-yne-3,17-diol, (17α)-

Levonorgestrel



Ethinyl Estradiol



SUPPORTING DOCUMENTS:

Type	Subject	Holder	Status	Review Date	Letter Date
DMF			Adequate	27 Aug 1998 K. Srinivasachar	N/A
DMF	Levonorgestrel		Adequate	5 Dec 1997 (M. Shaikh)	N/A
DMF	Ethinyl Estradiol		Adequate	16 April 1998 (D. Lin)	N/A

RELATED DOCUMENTS (if applicable): N/A

CONSULTS: Labeling and Nomenclature Committee

REMARKS/COMMENTS: . The Amendment of 11 Aug 1998 provides responses to the deficiency letter of 30 July 1998 and is the subject of this review.

CONCLUSIONS & RECOMMENDATIONS: The NDA may be approved from a chemistry, manufacturing and controls perspective. The Applicant should be informed that an 18 month expiration date for the product is acceptable based on the additional stability information provided. They should be reminded that this 18 month period is from the date of manufacture of the tablets and includes the storage time in bulk containers. The storage statement on the outer carton labels should be revised to include "[see USP *Controlled Room Temperature*]".

Orig. NDA 20-946
cc: HFD-580/Division File
HFD-580/ K. Srinivasachar/Rhee/CSO

/S/

K. Srinivasachar, Ph.D.
Review Chemist

R/D Init by: 8/28/98

filename: nda20946.3

KLSh

JUL 7 8 1998

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

NDA: 20-946
CHEMISTRY REVIEW # 1 **DATE REVIEWED:** 20 July 1998

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	26 Nov. 1997	1 Dec. 1997	4 Dec. 1997
AMENDMENTS	9 Feb. 1998	10 Feb. 1998	
	25 Mar. 1998	27 Mar. 1998	
	23 Apr 1998	24 Apr 1998	
	27 Apr 1998	28 Apr 1998	
	15 May 1998	18 May 1998	
	20 May 1998	21 May 1998	
	17 July 1998	20 July 1998	

JUL 2 8 1998

NAME & ADDRESS OF APPLICANT: Gynetics Inc.
198, Route 206, Somerville, NJ 08876

DRUG PRODUCT NAME
Proprietary: Preven Emergency Contraceptive Kit
Nonproprietary/Established/USAN: Levonorgestrel and Ethinyl Estradiol Tablets, USP
Code Name/#:
Chem.Type/Ther.Class: 3P

ANDA Suitability Petition / DESI / Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION: Progetin/Estrogen for emergency postcoital contraception.

DOSAGE FORM: Tablets
STRENGTHS: 0.25 mg Levonorgestrel/ 0.05 mg Ethinyl Estradiol
ROUTE OF ADMINISTRATION: oral
DISPENSED: X Rx __ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Molecular Formula: Levonorgestrel: $C_{21}H_{28}O_2$; Ethinyl Estradiol: $C_{20}H_{24}O_2$
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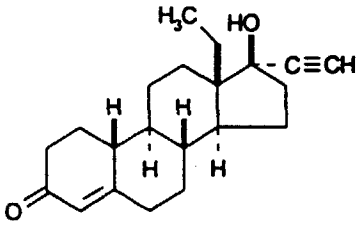
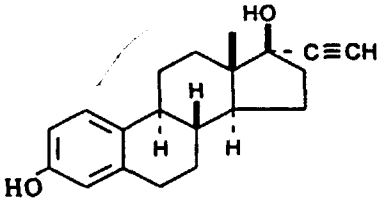
Chemical Name: Levonorgestrel: 18, 19-Dinorpregn-4-en-20-yn-3-one, 13-Ethyl-17-hydroxy-, (17α)-(-)
Ethinyl Estradiol: 19- Norpregn-1,3,5 (10) -triene-20-yne-3,17-diol, (17α)-

Levonorgestrel



Ethinyl Estradiol



SUPPORTING DOCUMENTS:

Type	Subject	Holder	Status	Review Date	Letter Date
DMF					
DMF	Levonorgestrel		Adequate	5 Dec 1997 (M. Shaikh)	N/A
DMF	Ethinyl Estradiol		Adequate	16 April 1998 (D. Lin)	N/A

RELATED DOCUMENTS (if applicable): N/A

CONSULTS: Labeling and Nomenclature Committee

REMARKS/COMMENTS: . The Amendment of 25 Mar 1998 provides the Tradename PREVEN for consideration because the original tradename PREVENT was found unacceptable by the Labeling and Nomenclature Committee. The name PREVEN was subsequently determined to be acceptable by the L & N Committee and will be the proprietary name for this drug product.

CONCLUSIONS & RECOMMENDATIONS: The NDA is approvable provided a satisfactory response is received to the comments and deficiencies in the draft letter at the end of this review.

/S/

K. Srinivasachar, Ph.D.
Review Chemist

Orig. NDA 20-946
cc: HFD-580/Division File
HFD-580/ K. Srinivasachar/Rhee/CSO

R/D Init by: 7/28/98

filename: nda20946.1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-946

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Kish

JUN 18 1998

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

NDA 20-946

SUBMISSION DATES: November 26, 1997
April 2, 1998

Prevent™ Emergency Contraceptive Kit
4 Levonorgestrel 0.25 mg/Ethinyl Estradiol 0.05 mg Tablets
and an urine pregnancy test
Gynetics Inc.
Princenton, NJ 08540

REVIEWER: Angelica Dorantes, Ph.D.

TYPE OF SUBMISSIONS: Original NDA

SYNOPSIS:

An Original NDA 20-946 for Prevent™ Contraceptive Kit (combination of four (4) levonorgestrel 0.25 mg/ethinyl estradiol 0.05 mg tablets and an urine contraceptive kit) was submitted on November 26, 1997 by Gynetics Inc. Prevent™ is intended for use as an emergency postcoital contraception. The levonorgestrel/ethinyl estradiol tablets contain botn a progestin and an estrogen and prevent pregnancy through the combined actions of the two hormones. The tablets are taken within 72 hours after unprotected sexual intercourse and is believed to prevent pregnancy by either preventing fertilization or by preventing the fertilized egg from implanting itself on the wall of the uterus, possibly as a result of impaired tubal function, altered uterine lining and prevention of normal hormonal ovarian secretions. If the pills are taken correctly, this method is thought to be about 75% effective.

II. RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed NDA 20-946 for Prevent™ Emergency Kit that was submitted on November 26, 1997. Based on the review of the overall information included in this submission, OCPB/DPEII is of the opinion that:

- The provided analytical and pharmacokinetic information is appropriate to support the approval of this NDA. However, it should be noted that Gynetic's Emergency Contraceptive Pill is not bioequivalent to the reference product, Ovral®. The upper limit of the % confidence interval (CI) for levonorgestrel's Cmax is %, which is outside of the Agency's % acceptance criteria. However, considering that the total dosage of levonorgestrel that is administered in one complete regimen of Gynetic's Emergency Contraceptive Pill is 1.0

mg and the maximum total dosage of levonorgestrel that is recommended in the postcoital emergency contraception regimens described in the Federal Register (see Attachment I) is 1.2 mg, then from the clinical pharmacology and biopharmaceutics perspective there are probably no safety or efficacy concerns for this product.

- The proposed *in vitro* dissolution method (USP Apparatus 2, 75 rpm, Medium: polysorbate 80 [5PPM] in water; 500 mL) is acceptable. However, the proposed release specifications of Q % at minutes for levonorgestrel and ethinyl estradiol are not justified by the provided dissolution data and therefore are not acceptable. The recommended release specifications for levonorgestrel and ethinyl estradiol are Q % at minutes.

- On April 2, 1998 Gynetics submitted an updated version of their proposed package insert for Prevent™ Emergency Contraceptive Kit. After review of the information included in the Pharmacokinetic section of the labeling, OCPB/DPEII recommends that the changes proposed on pages 12 to 14 of this bio-review be incorporated into the labeling. Revised labeling should be resubmitted for review.

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

/S/ 6/17/98

Angelica Dorantes, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics

RD Initialed by John Hunt. JPH 6/16/98

FT signed by John Hunt. /S/ 6/18/98

cc: NDA 20-946, HFD-580 (Ranick, Slaugther, Kish), HFD-870 (Chen, Dorantes), CDR (Barbara Murphy for Drug).

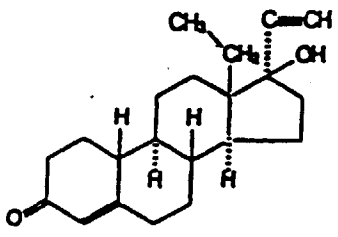
TABLE OF CONTENTS

III. BACKGROUND

Prevent™ Emergency Contraceptive Kit consists of blue film-coated tablets containing 0.25 mg levonorgestrel and 0.05 mg ethinyl estradiol and a urine pregnancy test. The Urine Pregnancy Test uses monoclonal antibodies to detect the presence of hCG (Human Chronionic Gonadotropin) in the urine.

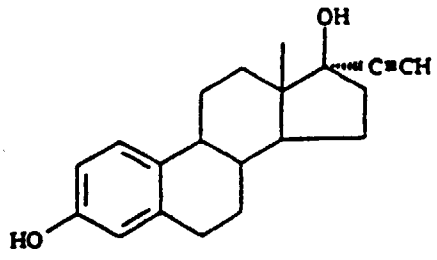
Levonorgestrel and ethinyl estradiol are USP monograph items that are commercially available. Their molecular weight, empirical formula, and chemical structure are described below.

LEVONORGESTREL



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

ETHINYL ESTRADIOL



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

In 1974, a Canadian researcher, Yuspe developed and studied a regimen of estrogen and progestin combination for post-coital contraception. This regimen consisted of two (2) tablets of 50 mcg ethinyl estradiol and 0.5 mg dl-norgestrel within 72 hours of unprotected sexual

intercourse followed by another two (2) tablets 12 hours later. This regimen is referred to as the "Yuspe method". In other studies, similar regimens have been studied by clinical researchers in the United States, Canada and many European countries. Reported effectiveness rates for the Yuspe regimen vary from 75% to 98% after one episode of unprotected intercourse. The only consistently reported side effects of treatment have been nausea and vomiting, occurring in about 50% and 25% of users, respectively. The Yuspe regimen is approved by the regulatory agencies of the United Kingdom, Germany, Sweden, Switzerland, and New Zealand. The most commonly prescribed off-label postcoital method in the United States is a large dose of the oral contraceptive, Ovral® (0.05 mg ethinyl estradiol/0.5 mg norgestrel).

On June 28, 1996, the Advisory Committee for Reproductive Health Drugs met to consider the safety and effectiveness of combined oral contraceptives for postcoital emergency use and unanimously concluded that the following four regimens are safe for postcoital emergency contraception. The four regimens are:

1. Take two (2) tablets of 0.05 mg ethinyl estradiol/0.5 mg norgestrel within 72 hours after unprotected intercourse, then take 2 more tablets 12 hours after the first dose;
2. Take four (4) 0.03 mg ethinyl estradiol 0.3 mg norgestrel within 72 hours after unprotected intercourse, then take 4 more tablets 12 hours after first dose;
3. Take four (4) tablets of 0.03 mg ethinyl estradiol/ 0.15 mg levonorgestrel within 72 hours after unprotected intercourse, then take 4 more tablets 12 hours after first dose;
4. Take four (4) tablets of 0.03 mg ethinyl estradiol/ 0.125 mg levonorgestrel within 72 hours after unprotected intercourse, then take 4 more tablets 12 hours after first dose.

On February 25, 1997 the Food and Drug Administration published a Federal Register Notice agreeing with the Advisory Committee conclusion and it requested the submission of new drug applications for postcoital emergency contraception.

The mechanisms by which these postcoital combination hormonal regimens prevent pregnancy are believed to be either prevention ovulation, preventing fertilization, interfering with implantation by altering the uterine lining, or suppression of gonadotropins.

In women taking a postcoital contraceptive, the total estrogenic level will be the result of estrogen from the contraceptive and endogenous estrogen from the ovaries and adipose tissue. Characteristically estrogen can be expected to have the following effects:

- Ovulation is inhibited in part by suppression of FSH and LH. In a sense, the pituitary gland is fooled into thinking a women is already pregnant and therefore does not release hormones to stimulate the ovary.
- Secretions within the uterus are altered as is the cellular structure of the endometrium leading to production of areas of edema alternating with areas of dense cellularity.

- Ovum transport is accelerated.
- Luteolysis, the degeneration of the corpus luteum, may occur at high levels of estrogen after local prostaglandins.

Progestins vary in both their inherent estrogenecity and their anti-estrogenic properties. Progestins vary in their androgenic effects, however, characteristically progestins can be expected to have the following effects:

- Ovulation is inhibited in part by suppression of LH.
- A thick cervical mucus is created, hampering the transport of sperm.
- Capacitation, the activation of enzymes that permit the sperm to penetrate the ovum, may be inhibited.

IV. DRUG FORMULATION

Only one strength of the combined progestin/estrogen (LNG 0.25 mg/EE 0.05 mg) product is proposed for marketing. The ECP is a blue film-coated immediate release tablet. The proposed to-be-marketed formulation made at the to-be-used manufacturing site was used in the only bio-study (No. ANA-97-105; Lot No. 7R89106, Batch size, tabs) conducted to support this NDA. Table 1 includes the formulation of the LNG/EE 0.25/0.05 mg tablets proposed to-be-marketed.

TABLE 2

Active Ingredients	*Input/Tablet*
Levonorgestrel, USP (micronized) Ethinyl Estradiol, USP (micronized)	0.0.25 mg 0.05 mg
Inactive Ingredients Core Tablet	
Anhydrous Lactose, NF (DT Grade) Polacrilin potassium, NF (Amberlite®IRP-88) Magnesium stearate, NF	mg mg mg
Theoretical Core Tablet Weight	mg
Film Coating Dispersion	mg*
Theoretical Coated Tablet Weight	mg

* Range 3-7 mg/tablet, target is 5 mg/tablet
**Not present in the finished product

V. *IN VITRO* METHODOLOGY

The proposed dissolution method is presented in Table 2.

TABLE 2

PROPOSED DISSOLUTION METHOD AND SPECIFICATIONS FOR PREVENT™ TABLETS	
Dosage Form:	Levonorgestrel/Ethinyl Estradiol Tablet
Strength(s):	0.25 mg levonorgestrel and 0.05 mg ethinyl estradiol
Apparatus Type:	
Media:	
Volume:	
Speed of Rotation:	
Sampling Time(s):	
Analytical Method:	
Release Rate Specifications:	

Table 3 presents a summary of the *in vitro* release test results for the lot used in the pivotal pharmacokinetic study.

TABLE 3

Study No.	Lot No.	Component	Sampling Times	% Dissolved Range	% Dissolved Mean	% CV
			min		86.0	5.4
		Levonorgestrel	min		92.4	1.7
			min		94.4	2.0
ANA-97-105	7R89106		min		96.2	2.4
			min		97.4	2.1
			min		98.3	2.2
			min		99.4	2.3
		Ethinyl Estradiol	min		99.2	2.8
			min		98.8	1.8
			min		99.5	2.6
			min		99.9	2.4
			min		99.1	1.4
			min		98.9	1.5
			min		99.5	2.8

REVIEWER COMMENT:

- It should be noted that the proposed *in vitro* dissolution test and dissolution specifications are the same as the ones described in *the 23 USP Official Monograph for Levonorgestrel and Ethinyl Estradiol Tablets*. Based on the provided dissolution data the sponsor's proposed specification of Q % at min for both levonorgestrel and ethinyl estradiol, is not justified and is not acceptable. It is recommended that the dissolution release specification for both levonorgestrel and ethinyl estradiol be changed to Q % at minutes.

VI. ANALYTICAL METHODOLOGY

COMMENT:

The validations for the analytical methodologies used for the determination of LNG and EE are adequate.

VII. CLINICAL PHARMACOLOGY AND BIOPHARMACEUTIC STUDIES

1. PHARMACOKINETICS:

Single Dose: The pharmacokinetic characteristics of the to-be-marketed product were characterized in one bio-study No. ANA-97-105. The objective of this study was to compare the bioavailability of Gynetics's Emergency Contraceptive Pill; Lot 7R89106 (Treatment A) with that of the Wyeth-Ayerst Canadian marketed product Ovral®; Lot 2EJW-B6 (Treatment B). It should be noted that levonorgestrel is the biologically active isomer of dl-norgestrel and therefore 250 µg of levonorgestrel is biologically equivalent to 500 µg of norgestrel. The study products were administered to Caucasian postmenopausal women (Age: 53±4 years, Weight: 59±7.5 Kg, Height: 158±6 cm) as 2 tablets of ECP (LNG 250 µg, EE 50 µg) or 2 tablets of Ovral® (norgestrel 500 µg, ethinyl estradiol 50 µg) as a single oral dose using a two-way crossover fasting study design and a 14 day wash out period between treatments. Thirty nine subjects entered the study but only thirty-five subjects completed the study (Period I: 39 subjects, Period II: 35 subjects). Blood samples were collected at specific times for 72 hours post-dose. Plasma was harvested from each blood sample and divided into four equal size aliquots. Two aliquots were assay for EE by

and the other two aliquots were assayed for LNG by the analytical division of

Figure 1 illustrates mean LNG and EE serum concentrations vs. time for ECP and Ovral®. Mean (SD) pharmacokinetic parameters are presented in Table 5.

FIGURE 1

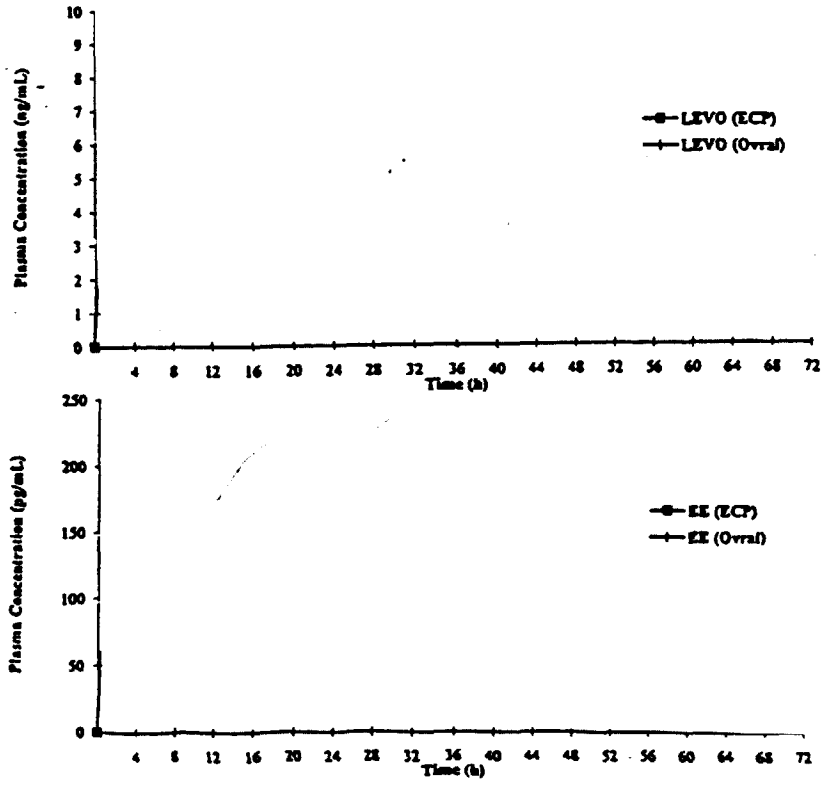


TABLE 5. Comparison of LNG and EE Pharmacokinetic Parameters

Compound	Study No. LNG/EE	Formulation	Cmax (ng/mL)	Tmax (h)	AUC0-t (ng/mL*h)	AUC0-inf (ng/mL*h)	Kel (h-1)	T1/2el (h)	F (%)
LNG	ANA-97-105	ECP	11 (4)	1.7 (1)	122.0 (53)	166.9 (92)	0.021 (.01	40.7 (19.2)	93.9
		Ovral®	9.2 (3.1)	2.0 (1.1)	121.4 (52)	177.8 (116)	0.019 (.01	45.4 (27.5)	
			(pg/mL)	(h)	(pg/mL*h)	(pg/mL)	(pg/mL*h)	(%)	(%)
EE	ANA-97-105	ECP	248.2 (67)	1.7 (.41)	2435 (630)	2747 (701)	0.038 (.01	21.2 (9.3)	96.5
		Ovral®	255.4 (72)	1.6 (.35)	2558 (749)	2848 (813)	0.039 (.01	20.1 (6.6)	

2. 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 100%) 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, the EE absolute bioavailability is about %.

b). ***Relative Bioavailability:*** A study comparing the bioavailability of the ECP with that of a reference product was conducted. The to-be-marketed formulation / product was used in the bio-study. Study ANA-97-105 compared the bioavailability of Gynetics's Emergency Contraceptive Pill; Lot 7R89106 (Treatment A) with that of the Canadian marketed product Ovral® ; Lot 2EJW-B6 (Treatment B). The results of this study showed that the relative bioavailability of levonorgestrel and ethinyl estradiol, as compared to an oral reference product, was % for both compounds.

c). ***Bioequivalence:*** The sponsor states that the purpose of study ANA-97-105 was to compare the bioavailability of the 2 products, not to determine bioequivalence in the usual way, since the two products are different in composition. However, the sponsor calculated the Agency's 90% confidence intervals for LNG and EE using ANOVA and the two-one sided t-test on the AUC and Cmax log transformed. The statistical results are presented in Table 6.

TABLE 6. Comparison of LNG and EE Pharmacokinetic Parameters

Compound	LNG (ECP)	LNG (Ovral®)	Ratio %	90% CI
Geometric AUC0-t (ng/mL*h)	122.0 (52.3)	121.4 (52.4)	97.88	94.0-101.9
Geometric AUC0-inf (ng/mL*h	166.9 (92.2)	177.8 (116)	94.37	89.8-99.2
Geometric Cmax (ng/mL)	10.98 (4.0)	9.16 (3.1)	117.8	108.9-127.3
Compound	**EE (ECP)**	**EE (Ovral®)**	**Ratio %**	**90% CI**
Geometric AUC0-t (pg/mL*h)	2435.1 (630.1)	2558.41 (748.8)	95.0	91.3-98.8
Geometric AUC0-inf (pg/mL*h	2747 (701.1)	2848.3 (813.3)	96.2	92.9-99.6
Geometric Cmax (pg/mL)	248.2 (66.9)	255.4 (72.3)	96.5	93.5-99.6

With the exception of LNG Cmax, all other parameters were found to be within the % confidence interval range.

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

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

3. SPECIAL POPULATIONS:

The PK were conducted in postmenopausal women. However, the target population (premenopausal women) was studied in the supportive (published) clinical studies included in the Federal Register.

4. DRUG METABOLISM:

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

Levonorgestrel: The most important metabolic pathways occur in the reduction of the Δ4-3-oxo group and hydroxylation at positions 2α, 10β, and 16β, followed by conjugation. Most of the metabolites that circulate in the blood are sulfates of 3α,5β-tetrahydro-LNG, while excretion occurs predominantly in the form of glucuronides. Some of the parent LNG also circulates as 17α-sulfate. Metabolic clearance rates may differ among individuals by several fold, and this may account in part for the high variability observed in levonorgestrel concentrations among users.

Ethinyl Estradiol: The cytochrome P-450 enzyme (CYP3A4) is responsible for the 2-hydroxylation that is the major oxidative reaction. The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and fecal excretion. Levels of Cytochrome P-450 vary widely among individuals and can explain the variation in rates of ethinyl estradiol 2-hydroxylation. Ethinyl estradiol is excreted in the urine and faeces as glucuronides and sulfates and undergoes enterohepatic circulation.

5. 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) Other drugs may decrease the effectiveness of EE or in a few 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 increases gut transit and cause diarrhea are potentially likely to reduce concentrations of ethinyl estradiol.
- *Interactions with metabolism:*

  Gastrointestinal Wall: The gastrointestinal wall has been shown to be a site for interaction for the sulfation of ethinyl estradiol which can result in the enhancement of the activity of this drug which may increase its bioavailability and result in side-effects. (i.e., ascorbic acid acts as competitive inhibitor for sulfation 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 which may decrease ethinyl estradiol plasma levels below therapeutic levels (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 that support the view that enterohepatic circulation of ethinyl estradiol decreases in women taking antibiotic agents such as ampicillin, tetracycline, etc.
- *Interference in the metabolism of other drugs:* Ethinyl estradiol can inhibit hepatic microsomal enzymes and therefore possibly 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.

7. PK/PD RELATIONSHIPS AND POPULATION PHARMACOKINETICS:

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

VIII. PROPOSED LABELING

The April 2, 1998 version of the proposed package insert is included in Attachment III

LABELING COMMENT: The following changes are recommended for the labeling:

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

ATTACHMENT I

Includes;

NDA 20-946

FEDERAL REGISTER

Vol. 62, No. 37/ Tuesday, February 25, 1997

federal register

Tuesday
February 25, 1997

Part V

Department of Health and Human Services

Food and Drug Administration

Prescription Drug Products; Certain Combined Oral Contraceptives for Use as Postcoital Emergency Contraception; Notice

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 96N-0492]

Prescription Drug Products; Certain Combined Oral Contraceptives for Use as Postcoital Emergency Contraception

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that the Commissioner of Food and Drugs (the Commissioner) has concluded that certain combined oral contraceptives containing ethinyl estradiol and norgestrel or levonorgestrel are safe and effective for use as postcoital emergency contraception, and requests submission of new drug applications (NDA's) for this use. This notice is intended to encourage manufacturers to make this additional contraceptive option available.

ADDRESSES: Submit NDA's to the Food and Drug Administration, Center for Drug Evaluation and Research, Central Document Room, 12229 Wilkins Ave., Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Lisa D. Rarick, Center for Drug Evaluation and Research (HFD-580), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-4260.

SUPPLEMENTARY INFORMATION:

I. Background

Combined oral contraceptives, which contain an estrogen and a progestin, were first approved in the United States in 1960 and in many other countries shortly thereafter. When taken daily for 3 weeks followed by a week without medication, these drugs provide effective contraception. They have become one of the most widely employed methods of pregnancy prevention, currently used by an estimated 11 million American women. In the period since the introduction of combined oral contraceptives, the amounts of estrogen and progestin have been reduced and explicit labeling guidance for safe use has been developed in response to extensive medical research. Consequently, combined oral contraceptives are now accepted as remarkably safe and effective when used as directed. There are more than 30 brands of FDA-approved oral contraceptives on the American market that contain estrogens and progestins. These products contain estrogens and progestins in different amounts and have some differences in labeling, but all are considered to be safe and effective.

For several decades, estrogens and progestins have also been used, either separately or in combination, to prevent pregnancy in women who have unprotected intercourse as a result of rape, contraceptive failure, or lack of planning. Such drugs, when used for this purpose, are known as emergency contraceptive pills, or postcoital pills, or morning-after pills.

The best researched regimen for emergency contraceptive pills was first described in 1974 by Professor A. Albert Yuzpe of Canada (Ref. 18). The regimen consists of two tablets, each tablet containing 0.05 milligram (mg) of ethinyl estradiol and 0.50 mg of norgestrel, taken within 72 hours after unprotected intercourse; a second identical dose is to be taken 12 hours after the first dose. When used in this manner, the treatment is 75 percent effective in preventing pregnancy.

This regimen and the very similar regimens described below are widely used. The specific regimen described by Yuzpe is approved for use by the drug regulatory agencies of the United Kingdom, Germany, Sweden, Switzerland, and New Zealand. The approved products used in this regimen contain ethinyl estradiol and, as the progestin, either norgestrel or levonorgestrel.

The Yuzpe regimen and similar regimens have been used extensively in the United States in the last two decades, even though no products are approved and labeled for this use. The drugs are prescribed by hospital emergency rooms, reproductive health clinics, and university health centers. They are also prescribed, although less widely, by physicians in private practice. On February 14, 1996, the Reproductive Health Technologies Project established a hotline number (1-800-584-9911) to inform women about this contraceptive method and about providers in their local area.

Since the United Kingdom approved emergency contraceptive pills in 1984, more than 4 million prescriptions have been recorded. However, the actual use is much greater because providers have found it less expensive to provide tablets of identical drugs taken from products packaged as combined oral contraceptives. The use of combined oral contraceptives for emergency contraception in the United States can only be estimated because they are not approved for this indication, but the results of a Kaiser Family Foundation survey reported at the June 28, 1996, meeting of FDA's Advisory Committee for Reproductive Health Drugs (the Advisory Committee) suggest that approximately 225,000 American women have used the method. A further indication of the extent of use is that over 25,000 calls were made to the hotline number (cited above) in the first 5 months of operation.

In November 1994, the Center for Reproductive Law & Policy filed a citizen petition asking FDA to require manufacturers of certain combined oral contraceptive products to amend their labeling and patient package inserts to include information regarding the use of these products for postcoital emergency contraception. Although FDA indicated that it had the authority to require that certain conditions of use be included in a product's labeling, it declined to exercise its discretion in this case to require the relabeling of these products for emergency contraception, and denied the petition. However, the agency decided to present the issue of the safety and effectiveness of combined oral contraceptives for postcoital emergency use to the Advisory Committee. The Advisory Committee met on June 28, 1996, to consider this issue and unanimously concluded that the four regimens below are safe and effective for postcoital emergency contraception. For the reasons described in section II. below, FDA agrees with this conclusion.

The four regimens for postcoital emergency contraception are as follows:

(1) For tablets that contain 0.05 mg of ethinyl estradiol and 0.50 mg of norgestrel, take 2 tablets within 72 hours after unprotected intercourse, then take 2 more tablets 12 hours after the first dose;

(2) For tablets that contain 0.03 mg of ethinyl estradiol and 0.30 mg of norgestrel, take 4 tablets within 72 hours after unprotected intercourse, then take 4 more tablets 12 hours after the first dose;

(3) For tablets that contain 0.03 mg of ethinyl estradiol and 0.15 of levonorgestrel, take 4 tablets within 72 hours after unprotected intercourse, then take 4 more tablets 12 hours after the first dose; and

(4) For tablets that contain 0.03 mg of ethinyl estradiol and 0.125 mg of levonorgestrel, take 4 tablets within 72 hours after unprotected intercourse, then take 4 more tablets 12 hours after the first dose.

The appendix to this notice provides information concerning the use of emergency contraceptive pills that might be useful to sponsors in drafting

physician and patient labeling for these products for this use.

II. Discussion

A. Safety

Experience with the approved products in Europe and New Zealand has demonstrated the regimens to be safe. At the Advisory Committee's June 28, 1996, meeting, Elizabeth Barden presented information from the British Medicines Control Agency that only six serious adverse reactions associated with these products for this use were reported to it from 1984 to 1996. Of these, only one occurred close enough to the time of administration to indicate that the reaction might be drug related.

Emergency contraceptive pills are not effective if the woman is pregnant; they act by delaying or inhibiting ovulation, and/or altering tubal transport of sperm and/or ova (thereby inhibiting fertilization), and/or altering the endometrium (thereby inhibiting implantation). Studies of combined oral contraceptives inadvertently taken early in pregnancy have not shown that the drugs have an adverse effect on the fetus, and warnings concerning such effects were removed from labeling several years ago. There is, therefore, no evidence that these drugs, taken in smaller total doses for a short period of time for emergency contraception, will have an adverse effect on an established pregnancy.

B. Effectiveness

There are numerous published articles that support the effectiveness of oral contraceptive pills for emergency use (Refs. 1, 3, 4, 7 through 14, 16 and 18 through 21). In 1996, Trussell, Ellertson, and Stewart reported a meta-analysis of 10 published articles on clinical trials of emergency contraceptive pills in which the number of pregnancies among women with regular menstrual cycles who used emergency contraception was compared to the expected number of pregnancies based on the cycle day of intercourse and published estimates of conception probabilities by cycle day (Ref. 9). Defining effectiveness as the percent reduction in the likelihood of pregnancy occurring, the authors found a range of effectiveness of 55.3 percent to 94.2 percent, with an average effectiveness of 74.0 percent. In other words, if 100 women have unprotected intercourse once during the second or third week of their menstrual cycle, about 8 will become pregnant, but if the same women use emergency contraception after intercourse, only 2 will become pregnant.

III. References

The following references have been placed on display in the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Bagshaw, S. N., D. Edwards, and A. K. Tucker, "Ethinyl Oestradiol and D-Norgestrel Is an Effective Emergency Postcoital Contraceptive: A Report of Its Use in 1,200 Patients in a Family Planning Clinic," *Australian and New Zealand Journal of Obstetrics and Gynecology*, 28:137–140, 1988.

2. Delbanco, S., "1995 Kaiser Family Foundation Surveys on Emergency Contraceptive Pills: Knowledge and Attitudes among American Adults and Obstetrician/Gynecologists," Testimony before the FDA Reproductive Health Drugs Advisory Committee, June 28, 1996.

3. Fasoli, M., F. Parazzini, G. Cecchetti, and C. La Vecchia, "Post-coital Contraception: An Overview of Published Studies," *Contraception*, 39:459–468, 1989.

4. Glasier, A., "Postcoital Contraception," *Reproductive Medicine Review*, 2:75–84, 1993.

5. Glasier, A., et al., "Mifepristone (RU486) Compared with High-Dose Estrogen and Progestogen for Postcoidal Emergency Contraception," *New England Journal of Medicine*, 327:1041–1044, 1992.

6. Haspels, A. A., and M. R. Van Santen, "New Aspects in Post-coital Contraception," in "Future Aspects in Contraception," edited by B. Runnebaum, T. Rabe, and L. Kiesel, MTP Press Limited, Boston, 1985.

7. Ho, P. C., and M. S. W. Kwan, "A Prospective Randomized Comparison of Levonorgestrel with the Yuzpe Regimen in Post-coital Contraception," *Human Reproduction*, 8:389–392, 1993.

8. Percival-Smith, R. K. L., and B. Abercrombie, "Postcoital Contraception with dl-Norgestrel/Ethinyl Estradiol Combination: Six Years Experience in a Student Medical Clinic," *Contraception*, 36:287–293, 1987.

9. Trussell, J., C. Ellertson, and F. Stewart, "The Effectiveness of the Yuzpe Regimen of Emergency Contraception," *Family Planning Perspectives*, 28:58–87, 1996.

10. Trussell, J., and F. Stewart, "The Effectiveness of Postcoital Hormonal Contraception," *Family Planning Perspectives*, 24:262–264, 1992.

11. Trussell, J., et al., "Emergency Contraceptive Pills: A Simple Proposal to Reduce Unintended Pregnancies," *Family Planning Perspectives*, 24:269–273, 1992.

12. Tully, B., "Postcoital Contraception—A Study," *British Journal of Family Planning*, 8:119–124, 1983.

13. Van Look, P. F. A., and H. von Hertzen, "Emergency Contraception," *British Medical Bulletin*, 49:158–170, 1993.

14. Van Santen, M. R., and A. Haspels, "Interception II: Postcoital Low-Dose Estrogens and Norgestrel Combination in 633 Women," *Contraception*, 31:275–293, 1985.

15. Webb, A., "Safety and Medical Contraindications," in "The Provision of Emergency Hormonal Contraception," edited by D. Paintin, ch. 4, RCOG Press, London, 1995.

16. Webb, A., J. Russell, and M. Elstein, "Comparison of Yuzpe Regimen, Danazol, and Mifepristone (RU486) in Oral Postcoital Contraception," *British Medical Journal*, 305:927–931, 1992.

17. Webb, A., and D. Taberner, "Clotting Factors After Emergency Contraception," *Advances in Contraception*, 9:75–82, 1993.

18. Yuzpe, A. A., et al., "Post Coital Contraception—A Pilot Study," *Journal of Reproductive Medicine*, 13:53–58, 1974.

19. Yuzpe, A. A., R. Percival Smith, and A. Rademaker, "A Multicenter Clinical Investigation Employing Ethinyl Estradiol Combined With dl-Norgestrel as a Postcoital Contraceptive Agent," *Fertility and Sterility*, 37:508–513, 1982.

20. Yuzpe, A. A., and W. J. Lancee, "Ethinylestradiol and dl-Norgestrel as a Postcoital Contraceptive," *Fertility and Sterility*, 28:932–936, 1977.

21. Zuliani, G., U. F. Colombo, and R. Molla, "Hormonal Postcoital Contraception with an Ethinylestradiol-Norgestrel Combination and Two Danazol Regimens," *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 37:253–260, 1990.

IV. Conclusions

The Commissioner has concluded that combined oral contraceptives, taken initially within 72 hours of unprotected intercourse and providing a total of 0.10 or 0.12 mg of ethinyl estradiol and 0.50 or 0.60 mg of levonorgestrel in each of 2 doses separated by 12 hours, are safe and effective for use as postcoital emergency contraception. The Commissioner bases this conclusion on FDA's review of the published literature concerning this use (listed above), FDA's knowledge of the safety of combined oral contraceptives as currently labeled, and on the unanimous conclusion that these regimens are safe and effective made by the agency's Advisory Committee for Reproductive Health Drugs at its June 28, 1996, meeting. Because such combined oral contraceptives have not been labeled for this use or this dosage regimen, the Commissioner finds that these products are new drugs as defined in section 201(p)(1) and (p)(2) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)(1) and (p)(2)). Accordingly, approved NDA's are required as a condition of marketing.

FDA is prepared to accept NDA's for combined oral contraceptives appropriately labeled for use as postcoital emergency contraception under section 505(b)(2) of the act (21 U.S.C. 355(b)(2)) and part 314 (21 CFR part 314). Because of the publicly available safety and effectiveness data documenting the drugs' use, the safety and effectiveness requirements of § 314.50 may be met by citing the

published literature listed in the references in section III. of this document. The Commissioner advises that it is unnecessary to submit copies and reprints of the data cited in section III. of this document. Both the safety and effectiveness data upon which the Commissioner bases the above conclusions and the minutes of the Advisory Committee meeting are on file for public inspection in the Dockets Management Branch (address above). The Commissioner invites applicants to submit any other pertinent studies and literature of which they are aware.

Dated: February 20, 1997.

David A. Kessler,

Commissioner of Food and Drugs.

Appendix

Use of Emergency Contraceptive Pills (ECP's)

ECP's consist of two doses of regular birth control pills containing estrogen and progestin. Taking ECP's provides a short, strong, burst of hormone exposure. Depending on where you are in your cycle and when you had unprotected intercourse, using ECP's may prevent ovulation, disrupt fertilization, or inhibit implantation of a fertilized egg in the uterus.

How To Use ECP's

The oral contraceptive pills that can be used as ECP's are listed below. Take only one type of pill, not all of them. For example, if you use Ovral, you do not need Nordette. If you are getting your ECP's from a regular pack of birth control pills containing 28 pills (1 for every day), remember that the last 7 (green or pink) pills do not contain any hormones.

Brand Name	Pill Color	Number of pills to swallow within 72 hours after unprotected sex	Number of pills to swallow 12 hours later
Ovral	white	2	2
Lo/Ovral	white	4	4
Nordette	light orange	4	4
Levlen	light orange	4	4
Triphasil	yellow	4	4
Tri-Levlen	yellow	4	4

1. Swallow the first dose no later than 72 hours after having unprotected sex. Remember that the second dose must be taken 12 hours after the first dose. Taking the first dose at 3 p.m. would mean taking the second dose at 3 a.m. So take the first dose at a time that will make it convenient to take the second dose 12 hours later.

2. Swallow the second dose 12 hours after taking the first dose. Do not swallow any extra ECP's. More pills will probably not decrease the risk of pregnancy any further and will increase the risk of nausea.

Side Effects of ECP's

About half the women who take ECP's have temporary nausea. It is usually mild and should stop in a day or so. The risk of nausea may be reduced if you take a long-acting nonprescription antinausea medicine (such as meclizine) 30 minutes to 1 hour before taking each of the two doses of ECP's. About 20 percent of women who take ECP's vomit. If you vomit within an hour after taking either dose of ECP's, call your clinician to discuss whether to repeat that dose or to take antinausea medicine.

Before Taking ECP's

If you think you might have gotten pregnant last month, see your clinician before taking ECP's. Early pregnancy symptoms can include breast tenderness, nausea, or a previous period that was not quite normal.

If you have a serious medical problem, talk to your clinician before using ECP's.

After Taking ECP's

Your next menstrual period may start a few days earlier or later than usual. If your period does not start within 3 weeks, see your clinician for an exam and pregnancy test. If ECP's fail, or if you were already pregnant when you took ECP's, the fetus would be exposed to hormones. Studies of women who continued to take birth control pills after they unknowingly became pregnant do not show any evidence of harm to the fetus.

ECP's may not prevent an ectopic pregnancy (in the tubes or abdomen). Ectopic pregnancy is a medical emergency. In ectopic pregnancies, spotting and cramping pain usually begin shortly after the first missed menstrual period. See your clinician immediately if you experience these symptoms.

After taking ECP's, get started as soon as you possibly can with a method of birth control you will be able to use every time you have sex. ECP's are meant for one-time, emergency protection. ECP's are not as effective as other forms of birth control. If you want to start or resume use of birth control pills after taking ECP's, consult your clinician. Protect yourself from Acquired Immune Deficiency Syndrome (AIDS) and other sexual infections as well as pregnancy. Use condoms every time you have sex if you think you may be at risk.

Source: Adapted (with permission) from Trussell, J., F. Stewart, F. Guest, and R. A. Hatcher, "Emergency Contraceptive Pills: A Simple Proposal To Reduce Unintended Pregnancies," *Family Planning Perspectives*, 24:269–273, 1992.

[FR Doc. 97–4663 Filed 2–24–97; 8:45 am]

BILLING CODE 4160–01–F

Kish AUG 13 1998

Clinical pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA:	20-946
DRUG:	Preven™ Emergency Contraceptive kit 4 Levonorgestrel 0.25 mg/Ethinyl Estradiol 0.05 mg tablets and an urine pregnancy test
SPONSOR:	Gynetics Inc.
SUBMISSION DATE:	7/13/98
TYPE OF SUBMISSION:	Sponsor's Response
REVIEWER:	Venkateswar R. Jarugula, Ph.D.

SYNOPSIS

The original NDA 20-946, which was submitted on 11/26/97 was reviewed by the Office of Clinical Pharmacology and Biopharmaceutics and the recommendations were conveyed to the sponsor in the agency's letter dated 7/8/98 (see FDA letter in Attachment I). In the current submission, the sponsor included their response to FDA recommendations. The purpose of this review is to evaluate the adequacy of sponsor's response to the previous recommendations.

In Vitro Release Specification:

In response to the recommendation to revise the release specification, sponsor agreed to incorporate the requested specification of Q: % at minutes for levonorgestrel and ethinyl estradiol into the release specifications for all batches of the drug product.

Labeling revision:

Sponsor stated that all the changes requested by the division were incorporated in the revised labeling submitted for review in the current submission. However, several deficiencies have been identified and those deficiencies need to be corrected as outlined below.

Reviewer Comments on labeling revision:

1. In Table 1, the units for C_{max} and AUC should be corrected as pg/mL and pg/mL*h, respectively, for ethinyl etsradiol.

2. Under 'Excretion' section, please include the units for the half-life of ethinyl estradiol.

3. Drug-Drug Interactions section should be revised as follows:

   - The second sentence in the first paragraph should be replaced by

   - Second sentence in Absorption interactions subsection should be replaced by

   - The first sentence in Gastrointestinal Wall subsection should be replaced by

RECOMMENDATION

The sponsor's response to the FDA recommendations is acceptable provided the Clinical Pharmacology section of the labeling is revised as recommended in Reviewer Comments 1 to 3.

/S/ 8/13/98

Venkateswar R. Jarugula, Ph.D.

RD initialed by Ameeta Parekh, Acting Team Leader, Ph.D. /S/ 8/13/98

FT initialed by Ameeta Parekh, Acting Team Leader, Ph.D. /S/ 8/13/98

cc: NDA 20-946, HFD-580 (Slaughter, Kish), HFD-870 (M.chen, Dorantes, Jarugula), CDR (B.Murphy for Drug).

ATTACHMENT I
(FDA letter dated 7/8/98)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-946

ADMINISTRATIVE DOCUMENTS

DF

JUL 8 1998

NDA 20-946

Gynetics Inc.
Attention: Ms. Margaret P. Filipiak
Regulatory Manager
56 Locust Lane
Princeton, NJ 08540

Dear Ms. Filipiak:

Please refer to your pending November 26, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Preven (levonorgestrel and ethinyl estradiol) Tablets.

We also refer to your submission dated April 2, 1998.

We have completed our review of the Clinical Pharmacology and Biopharmaceutics section of your submission and have the following comments and information requests:

1. The proposed release specifications (Q % at minutes) for levonorgestrel and ethinyl estradiol are not justified by the dissolution data provided in your application. A revised release specification of Q % at minutes should be submitted.

2. Revisions to the CLINICAL PHARMACOLOGY section of your Prescribing Insert are enclosed. Revised labeling incorporating these changes should be submitted for review as soon as possible.

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

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. In addition, we may identify other information that must be provided prior to approval of this application. If you respond in the current review cycle we may or may not consider your response prior to taking an action on your application. In the meantime, we are continuing our review of your application.

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

Sincerely,

/S/

7/7/98

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

ENCLOSURE
Biopharmaceutic Labeling Revisions

Group Leader Memorandum SEP 01 1998

NDA:	20-946
Drug :	Preven™
Sponsor:	Gyne'tics
Drug Description:	Ethinyl estradiol (.05 mg) plus levonorgestrol (0.25 mg) in a tablet formulation packaged as 4 pills in a blister package.
Dosage:	Patient are instructed to take a dose of two tablets orally as soon as possible following unprotected intercourse, and two additional tablets 12 hours after the first dose.
Proposed Indication:	Emergency contraception to prevent pregnancy
NDA Submitted:	November 26, 1997
NDA Received:	December 1, 1998
Major Amendment:	April 27, 1998
NDA Completed:	September 1, 1998
Date of Memorandum:	September 1, 1998

The sponsor submitted this application in response to the February 25, 1997 Federal Register Notice regarding the use of certain combined oral contraceptives for use as postcoital emergency contraception. In the concluding statements of this document it was stated that:

> "combined oral contraceptives, taken initially within 72 hours of unprotected intercourse and providing a total of 0.10 or 0.12 mg ethinyl estradiol and 0.50 or 0.60 mg of levonorgestrel in each of 2 doses separated by 12 hours, are safe and effective for use as postcoital emergency contraception."

Preven™ meets these criteria, and is the first product to be submitted as a NDA for this indication. The submission consists of chemistry information (manufacturing, controls, stability) and data to demonstrate bioequivalence to an approved oral contraceptive Ovral®. In addition, clinical information was submitted which included published literature supporting the efficacy and safety of the ethinyl estradiol/levonorgestrol combination when used as an emergency contraceptive. This information supports the approval of Preven™ as an emergency contraceptive.

Clinically, this NDA review consisted primarily of writing a product label which adequately desribes the safe and effective use of the Preven™ for the indication of postcoital emergency contraception. Multiple drafts of the labeling have been submitted and discussed in detail with the sponsor. The draft labeling which the sponsor submitted on 9/1/98 is acceptable. Therefore, I recommend approval of this NDA.

/S/

Marianne Mann M.D., Deputy Director, HFD-580

cc:
HFD-580/Rarick, Slaughter
NDA 20-946

NDA 20-946
Preven (levonorgestrel and ethinyl estradiol tablets
and pregnancy test)
Gynetics Inc.

Division Directors Memo

This application will be signed off at the Division level. Therefore, a Division Directors Memo is not required.

NDA 20-946
Preven (levonorgestrel and ethinyl estradiol tablets
and pregnancy test)
Gynetics Inc.

Pharmacology Review

The safety and effectiveness of this application relies on published literature designated in the Federal Register Notice of February 25, 1997, therefore a Pharmacology review is not required.

NDA 20-946
Preven (levonorgestrel and ethinyl estradiol tablets
and pregnancy test)
Gynetics Inc.

Safety Update Review

This application relies on published clinical trial data designated by the Agency as adequate to support this indication. Therefore, a Safety Update and Safety Update Review are not required.

NDA 20-946
Preven (levonorgestrel and ethinyl estradiol tablets
and pregnancy test)
Gynetics Inc.

Statistical Review

The clinical and statistical sections of this application are based on published clinical trials designated by the Agency as sufficient to support this indication. Therefore, a statistical review is not required.

NDA 20-946
Preven (levonorgestrel and ethinyl estradiol tablets
and pregnancy test)
Gynetics Inc.

Microbiology Review

This application provides for an oral tablet, therefore a microbiology review is not necessary.

NDA 20-946
Preven (levonorgestrel and ethinyl estradiol tablets
and pregnancy test)
Gynetics Inc.

Advertising Material

Advertising material for this application has not yet been submitted for review.

NDA 20-946
Preven (levonorgestrel and ethinyl estradiol tablets
and pregnancy test)
Gynetics Inc.

DSI Audit of Clinical Studies

This application's clinical section is based on literatures citations of studies designated by the Agency as adequate to support this indication. Therefore, no clinical audits are required.

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.

A/BLA # 20-996 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD 580 Trade and generic names/dosage form: _____ (levonorgestrel & ethinyl estradiol) Action: AP AE NA

Applicant Gynetics Inc Therapeutic Class _____

Indication(s) previously approved Contraception

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

Proposed indication in this application Emergency 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) ✓ 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 __ No

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

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

/S/ _____ 3/17/98

Signature of Preparer and Title Date

Orig NDA/BLA # 20-996
HFD-580 /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)

Kish

JAN 5 1998

MEMORANDUM

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

DATE: January 5, 1998

FROM: Angelica Dorantes, Ph.D., Team Leader
Office of Clinical Pharmacology and Biopharmaceutics A Dorantes 1/5/98

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

ISSUE: Filing of NDA 20-946 for PREVENT™ (Emergency Contraception Kit)

SYNOPSIS

On November 26, 1997, Gynetics, Inc. submitted NDA 20-946 for PREVENT™ (Emergency Contraceptive Kit). The PREVENT™ kit consists of emergency contraceptive pills (0.25 mg levonorgestrel and 0.05 mg ethinyl estradiol tablets) and a urine pregnancy kit. The emergency contraceptive pills are indicated for the prevention of pregnancy in women who have had unprotected intercourse since their last menstrual period. Emergency pills are not effective if the women is pregnant; they act primarily by inhibiting ovulation, and/or altering tubal transport of sperm and/or ova (thereby inhibiting fertilization), and/or altering the endometrium (thereby inhibiting implantation).

It should be noted that the clinical and statistical information included in this NDA follows the requirements outlined in the February 25, 1997 Federal Register Notice, that specifically states, "Because of the publicity available safety and effectiveness data documenting the drugs' use, the safety and effectiveness requirements of Sec. 314.50 may be met by citing the published literature listed in the references in section III of this document". Therefore, this NDA submission consists mainly of the Chemistry, Manufacturing and Controls section, the Human Pharmacokinetics and Bioavailability section, and the proposed labeling.

The Human Pharmacokinetics and Bioavailability section submitted to support the approval of PREVENT™ includes; drug formulation, analytical validation data, *in vitro* dissolution information, and bioavailability/bioequivalence data. The provided PK study compares the Gynetics' Emergency

Contraceptive Pill (ECP) with the Canadian Ovral®. The results of this study indicate that Gynetics' ECP is bioequivalent in every respect to Ovral® with the exception of levonorgestrel's Cmax (confidence intervals 109-127%).

RECOMMENDATION:

From the clinical pharmacology and biopharmaceutics viewpoint the NDA 20-946 dated November 26, 1997, is fileable provided the sponsor provides the following information;

1. The Clinical Pharmacology section of the labeling needs to be revised according to the current internal labeling guideline to include a Pharmacokinetic subsection describing the absorption, distribution, metabolism, excretion, etc. of the Emergency Contraceptive Pill.
2. It is recommended that the overall summaries and summary tables included in the Human Pharmacokinetic and Biopharmaceutic section and the proposed labeling be also submitted in electronic disks (preferable Word and Excel files).
3. Lastly, it should be noted that the pages of the NDA's overall index were not included.

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cc: NDA 20-946, HFD-580 (Kish), HFD-870 (Dorantes), CDR (B. Murphy for Drug)

EXCLUSIVITY SUMMARY for NDA # 20-946 SUPPL #_____

Trade Name Reven **Generic Name** levonorgestrel & ethinyl estradiol Tablets
Applicant Name Gynetics **HFD-** 580

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 /✓/ approval based on pivotal bioavailability study

   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?

_____

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 # 20-860 _____

NDA # 18-666 _____

NDA # 19-192 _____

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: The safety & effectiveness of these drugs are based on literature referenced in the Federal Register Notice of 2/25/97

(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 # based on published lit

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 # _____

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/

Signature
Title: CSO

8/26/98
Date

/S/

Signature of Division Director

9/1/98
Date

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

GYNÉTICS®

Patent Information

Under 21 CFR 314.53 (a), and according to 21 CFR 314.53 (2) there are no patents which claim the drugs or the drug product or which claim a method of using the drug product and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

Roderick L. Mackenzie
President
Gynétics Inc.

Gynétics Inc. • Suite 203 • 105 Raider Boulevard • Belle Mead, NJ 08502-1510
Telephone (908) 359-2429 • Fax (908) 359-6660

GYNÉTICS®

16.00001

NDA for Levonorgestrel and Ethinyl Estradiol Tablets, USP

Gynétics Inc. hereby certifies that it did not and will not use in any capacity the services of any person (including a corporation, partnership, association, or individual) debarred under subsection (a) or (b) [Section 306 (a) or (b)] in connection with this submission. [Section 306(k) (1) of the Generic Drug Enforcement Act of 1992 {21 USC 335 a (k) (1)}]

Gynétics Inc. hereby certifies that neither the Applicant nor any affiliated person(s) responsible for the development or submission of this application has been convicted of any relevant crime or offense for which they are subject to debarment.

10/2/97
Date

/S/
Roderick L. Mackenzie
Chairman of Gynétics Inc.

Gynétics Inc. • P.O. Box 8509 • Somerville, NJ 08876
Telephone (908) 359-2429 • Fax (908) 359-6660

Consult 850
940

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention : Dan Boring, Chair, HFD-530, Corporate Building, Room N461

From: Division of Reproductive and Urologic Drug Products. HFD-580
Attention: K. Srinivasachar, Ph.D. Phone: 827-4248

Date: 8 Jan. 1998

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: PREVENT NDA # 20-946

Established name, including dosage form: Levonorgestrel and Ethinyl Estradiol Tablets

Other trademarks by the same firm for companion products:

Indications for Use (may be a summary if proposed statement is lengthy): Emergency postcoital contraception

Initial comments from the submitter (concerns, observations, etc.): this is an emergency contraceptive kit consisting of 4 levonorgestrel 0.25 mg/ ethinyl estradiol 0.05 mg tablets and a urine pregnancy test.

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev Oct. 1993

CONSULT #940

LNC TRADEMARK REVIEW

TO: HFD-530

ATTN: K. Srinivaschar, Ph.D.

PROPOSED NAME(S): PREVENT

ESTABLISHED NAME: levonorgestrel and ethinyl estradiol tablets

COMMITTEE'S COMMENTS:

A review revealed one name which looks like or sounds like the proposed name: Proventil. The Committee believes the proposed name is sufficiently close to Proventil to be misleading as defined in 21 CFR 201.10(c)(5).

In addition, the Committee considers the proposed name may be misleading as defined in 21 CFR 201.10(c)(3), in that the name PREVENT implies a definite efficacy, when in fact this may not be the case.

For the reasons stated, the Committee finds the proposed name unacceptable.

/S/ 3/1/98

Dan Boring, Ph.D., Chairman
Labeling and Nomenclature Committee

AUG 27 1998

MEMORANDUM

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

FROM: Venkateswar R. Jarugula,
Clinical Pharmacology and Biopharmaceutics Reviewer,
(HFD-870) _____ 8/27/98

THROUGH: John Hunt, Deputy Director, Division of Pharmaceutical
Evaluation II, (HFD-870) _____ 8/27/98

TO: NDA 20-946/Preven™

RE: Labeling Revision

Synopsis

The original NDA 20-946, which was submitted on 11/26/97 was reviewed by the Office of Clinical Pharmacology and Biopharmaceutics and the labeling recommendations were conveyed to the sponsor in the FDA letters dated 7/8/98 and 8/18/98 (see attached letter). Sponsor submitted the revised labeling on 8/20/98 in response to the agency's earlier recommendations. The purpose of this memo is to comment on the adequacy of the revisions made to Clinical Pharmacology section of labeling (see attached labeling).

Sponsor has adequately incorporated all the changes recommended in the agency's letter dated 8/11/98.

Recommendation

The revised Clinical Pharmacology section of labeling for NDA 20-946 submitted on 8/20/98 is acceptable from Clinical Pharmacology perspective.

cc: NDA 20-946, HFD-580 (Slaughter, Kish), HFD-870 (M.Chen, Parekh), CDR(B.Murphy for Drug)

Kish

NDA 20-946

AUG 1 1 1998

Gynetics Inc.
Attention: Ms. Margaret P. Filipiak
Regulatory Manager
56 Locust Lane
Princeton, NJ 08540

Dear Ms. Filipiak:

Please refer to your pending December 1, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Preven Emergency Contraceptive Kit (levonorgestrel and ethinyl estradiol) Tablets.

We have completed our review of the Clinical section of your submission and have the following comments and information requests:

> Revisions to the Prescribing Insert, Detailed Patient Labeling and Patient Information Booklet are enclosed. Revised labeling incorporating these changes should be submitted for review as soon as possible.

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

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

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

Sincerely,

/S/ 8/12/98

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

ENCLOSURE
Clinical Labeling Revisions
CDRH consult
Clinical Pharmacology Labeling Revisions

cc:
Orig. NDA
HFD-580
HFD-580/SSlaughter/MMann/LRarick
HFD-580/CKish/8.11.98/n20946clb
concurrence:SSlaughter 8.11.98/MMann 8.11.98

INFORMATION REQUEST (IR)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-946

AUG 18 1998

Gynetics Inc.
Attention: Ms. Margaret P. Filipiak
Regulatory Manager
56 Locust Lane
Princeton, NJ 08540

Dear Ms. Filipiak:

Please refer to your pending November 26, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Preven (levonorgestrel and ethinyl estradiol) Emergency Contraceptive Kit.

We also refer to your submission dated July 17, 1998, which provided for a response to our letter dated July 8, 1998.

We have completed our review of your submission and have the following comments regarding the revisions to your **CLINICAL PHARMACOLOGY** section of the Prescribing Insert.

1. Table 1 entitled
should be revised such that the units for C_{max} and AUC of ethinyl estradiol are listed as pg/mL and pg/mL*h, respectively.

2. Within the subsection *"Excretion"*, units for the half-life of ethinyl estradiol should be included.

3. The subsection should be revised as follows:

   a. The second sentence of the first paragraph should be replaced with the following:

   b. The second sentence under the subheading should be replaced by the wording:

c. The first sentence in the subheading should be replaced by the following:

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

These comments are being provided to you prior to completion of our review of the applications to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application are finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

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

Sincerely,

/S/

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-946

JUL 30 1998

Gynetics Inc.
Attention: Ms. Margaret P. Filipiak
Regulatory Manager
56 Locust Lane
Princeton, NJ 08540

Dear Ms. Filipiak:

Please refer to your pending November 26, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Preven (levonorgestrel and ethinyl estradiol) Tablets.

We have completed our review of the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests:

1. The specification limits for impurities should be justified on the basis of actual levels observed in the various lots for ethinyl estradiol. Data should be provided to support the contention that the ethinyl estradiol used to manufacture the drug product is not a mixture of polymorphic forms; in particular, the absence of the form melting in the range ° C (USP 23, ethinyl estradiol monograph) should be established. The Certificate of Analysis from should state the levels of impurities actually determined in accordance with the updated impurity specifications in Drug Master File.

2. Based on the data submitted, a 6-month expiration date can be tentatively granted for drug product in bulk containers stored at 25°C and a 12-month expiration date can be granted for the drug product packaged in the proposed blister packs. The 12-month expiration date should be from the time of manufacture of the tablets and should include the storage time in bulk containers.

3. Because estrone is not observed in the stability results for the biobatch, which is more representative of the proposed commercial batches than the trial batch, it should not be specified.

4. The data provided support a tightening of the specification limit for individual impurities to not more than %. The revised specifications recommended for Impurities/Degradation products are:

   Individual not more than %; and
   Total not more than %.

5. Major impurities/degradation products should be structurally identified.

6. Clarification of whether the specifications for impurities/degradation products include process related impurities from the drug substances should be provided.

7. The reason for the fading of the blue color of the tablets at °C/ % RH should be investigated and an explanation as to why this is only observed for the biobatch should be provided.

8. Because of the revisions to the analytical methods for impurities/degradation products in ethinyl estradiol and the drug product, a new methods validation package should be submitted.

9. Storage conditions should be stated in the **HOW SUPPLIED** section of the labeling.

10. The storage statement on the carton labels should be revised to read °C ° F); excursions permitted to ° C ° F)" [see USP 23, page 11, *"Controlled Room Temperature"*].

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

These comments are being provided to you prior to completion of our review of the applications to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application are finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

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

Sincerely,

/S/

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader,
Division of Reproductive and Urologic
Drug Products (HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Kish

JUL 8 1998

NDA 20-946

Gynetics Inc.
Attention: Ms. Margaret P. Filipiak
Regulatory Manager
56 Locust Lane
Princeton, NJ 08540

Dear Ms. Filipiak:

Please refer to your pending November 26, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Preven (levonorgestrel and ethinyl estradiol) Tablets.

We also refer to your submission dated April 2, 1998.

We have completed our review of the Clinical Pharmacology and Biopharmaceutics section of your submission and have the following comments and information requests:

1. The proposed release specifications (Q % at minutes) for levonorgestrel and ethinyl estradiol are not justified by the dissolution data provided in your application. A revised release specification of Q % at minutes should be submitted.

2. Revisions to the **CLINICAL PHARMACOLOGY** section of your Prescribing Insert are enclosed. Revised labeling incorporating these changes should be submitted for review as soon as possible.

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

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. In addition, we may identify other information that must be provided prior to approval of this application. If you respond in the current review cycle we may or may not consider your response prior to taking an action on your application. In the meantime, we are continuing our review of your application.

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

Sincerely,

/S/

7/7/98

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

ENCLOSURE
Biopharmaceutic Labeling Revisions

cc:
Archival NDA 20-946
HFD-580/Div. Files
HFD-580/ADorantes/LRarick
DISTRICT OFFICE
HFD-580/CKish/6.30.98/n20946.bir
concurrence:ADorantes 6.30.98/LPauls 7.2.98/LRarick 7.7.98

INFORMATION REQUEST (IR)

Kish

NDA 20-946

MAY 15 1998

Gynetics Inc.
Attention: Ms. Margaret P. Filipiak
56 Locust Lane
Princeton, NJ 08540

Dear Ms. Filipiak:

We acknowledge receipt on April 28, 1998, of your April 27, 1998, amendment to your new drug application (NDA) for Preven (levonorgestrel and ethinyl estradiol) Emergency Contraceptive Kit.

We consider this a major amendment received by the Agency within three months of the user fee due date. Therefore, the user fee clock is extended three months. The new due date is September 1, 1998.

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

Sincerely yours,

/S/ 5/14/98

Lana Pauls M.P.H.
Chief, Project Management Staff
Division of Reproductive
and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA
HFD-580
HFD-580/LPauls/CKish
DISTRICT OFFICE
HFD-580/CKish/5.6.98/n20660ex
concurrence:LPauls 5.11.98/LRarick 5.8.98

REVIEW EXTENSION

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-946

Gynetics, Inc.
Attention: Ms. Margaret P. Filipiak
56 Locust Lane
Princeton, NJ 08540

DEC 3 1997

Dear Ms. Filipiak:

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:	Prevent™ Emergency Contraceptive Kit
Therapeutic Classification:	Priority
Date of Application:	November 26, 1997
Date of Receipt:	December 1, 1997
Our Reference Number:	20-946

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 January 30, 1998, in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact Christina Kish, Project Manager, 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/

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 20-946
HFD-580/Div. Files
HFD-580/CSO/C.Kish
HFD-580/HJolson/AJordan/MRhee/ADorantes
DISTRICT OFFICE

Drafted by: LPauls for CKish/December 3, 1997/N20946ac.001
Final:

ACKNOWLEDGEMENT (AC)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-946

CORRESPONDENCE

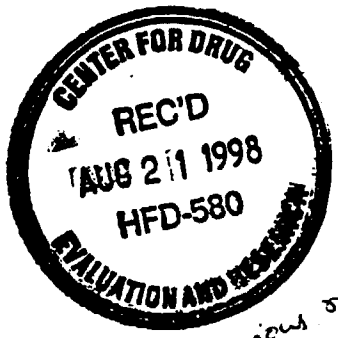
NDA # 20-946
Amendment # 015
August 20, 1998

ORIG AMENDMENT DUPLICATE

Margaret P. Filipiak
Pharmaceutical Regulatory Affairs

Phone: 609 924 4808
Fax: 609 252 0469
e-mail: magfil@aol.com

56, Locust Lane
Princeton, NJ 08540



August 20, 1998

Lisa Rarick, MD
Division of Reproductive and Urologic Drug Products (HFD 580)
Food and Drug Administration
5600 Fishers Lane,
Rockville, MD 20857-1706

Dear Dr. Rarick,

All previous recommended changes have been incorporated. – VRJ 8/24/98.

Re: NDA # 20-946 / Gynétics Inc./ PREVEN™ Emergency Contraceptive Kit/ Amendment # 015

Reference is also made to the letter received from the Agency on August 11, 1998 which requested revisions to the Prescribing Insert (PI), Detailed Patient Labeling (DPL) and Patient Information Book (PIB). We also provide a copy of the labeling without the highlighted changes for the convenience of the reviewer.

We herewith submit revised labeling incorporating changes to the PI, DPL and PIB. Most of the changes in the revised labeling are to obtain consistency between the PI, DPL and PIB. We have "blacklined" changes to the Division's suggested labeling to highlight the changes we are making to the labeling. We also need to add references back into the labeling to maintain a reasonable product liability protection position. The positioning of the pregnancy test is also an important part of the product liability protection program. In the interests of time, we are providing only the text with changes at this time. We will provide annotated labeling with references by early next week.

We need to communicate product efficacy in a manner which is consistent with virtually every published clinical efficacy study on ECPs, consistent with medical profession understanding and, consistent with patient understanding. When "efficacy" is stated as, e.g., a pregnancy rate reduction of 75%, the conclusion of 25% failure is virtually automatic. Planned Parenthood Federation of America, the foremost provider and organized authority on contraceptives in the US concluded in its web site (see attached print-out) that the failure rate of ECPs was 25%. Accordingly, efficacy needs to be stated as "a failure rate of 2%" and / or "about 2 out of 100 women may become pregnant after taking ECPs. This is a reduction of 75% in pregnancy rate" (re; Trussel 1998).

NDA # 20-946
Amendment # 015
August 20, 1998

If the Division would like to discuss any of the changes in the labeling, either by teleconference or by a meeting if this would be beneficial, please contact the undersigned.

This amendment is submitted in duplicate, one copy of the labeling in the archival copy and four copies in the review copy.

Yours sincerely,

Margaret P. Filipiak

Margaret P. Filipiak
For Gynétics Inc.

Copy: Gynétics Inc.

GYNÉTICS®

Roderick L. Mackenzie
Chairman of the Board

Via FedEx Overnight

August 11, 1998

Lisa Rarick, M.D.
Food & Drug Administration
5600 Fishers Lane
Room 14B04
Rockville, MD 20857

Dear Lisa:

Attached is a copy of the letter which we just sent responding to questions from the chemist for the PREVEN™ Emergency Contraceptive Kit. We have not added the attachments to this.

Lisa, we are very concerned with the implications of an approval for the PREVEN™ Emergency Contraceptive Kit with a limited dating of 12 months. Our concern is because this would definitely cause a limitation in distribution and availability of this emergency contraceptive product in retail pharmacies. This limited distribution during the early months of product availability could severely limit the utilization of emergency contraception by American women.

The data in the PREVEN™ formulations' stability package are strong. If these data were part of a generic drug submission for an oral contraceptive, an expiry dating of 18 to 24 months would be justified. These are well known drugs in a well known formulation.

We would strongly urge your support of a minimum dating on the PREVEN™ Emergency Contraceptive Kit of 18 months. We hope you can support this.

Sincerely,

R. L. Mackenzie

RLM/jm

cc: Christina Kisch (FDA)
Margaret Filipiak

Gynétics Inc. • Suite 203 • 105 Raider Boulevard • Belle Mead, NJ 08502-1510
Telephone (908) 359-2429 • Fax (908) 359-6660

ORIGINAL

Margaret P. Filipiak
Pharmaceutical Regulatory Affairs

Phone: 609 924 4808
Fax: 609 252 0469
e-mail: magfil@aol.com

56, Locust Lane
Princeton, NJ 08540

ORIG AMENDMENT
3L

August 29, 1998

Lisa Rarick, MD
Division of Reproductive and Urologic Drug Products (HFD 580)
Food and Drug Administration
5600 Fishers Lane,
Rockville, MD 20857-1706

Dear Dr. Rarick,

Re: NDA # 20-946 / Gynétics Inc./ PREVEN™ Emergency Contraceptive Kit/ Amendment # 017

Reference is also made to the labeling revisions faxed to us yesterday, August 28,1998 and the subsequent telephone conference call between Mr. Roderick Mackenzie, Mr. Gregg Clements, Mr. Gerald Meyer, and the undersigned representing Gynétics and Dr. Lisa Rarick, Dr. Marianne Mann, Dr. Susan Allen and Mr. Randy Olmstead representing the FDA.

Gynétics agreed to omit the references as strongly recommended by the Agency in the August 27th letter from the Agency. The Agency agreed that reference 9 could be omitted from the "Efficacy Table". Agreement was reached to omit the Drug-Drug Interactions from the Detailed Patient Labeling. It was agreed that there was clinical support to include in the labeling that the ECPs should be taken as soon as conveniently possible. The PI, Detailed Patient Labeling and the Patient Information Book are attached to reflect the changes.

This amendment is submitted in duplicate.

Yours sincerely,

Margaret P. Filipiak

Margaret P. Filipiak
For Gynétics Inc.

Copy: Gynétics Inc

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE