CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 20946/S001

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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20946/S001

Trade Name: Preven Emergency Contraceptive Kit

Generic Name: (levonorgestrel/ethinyl estradiol)

Sponsor: Gynetics, Inc.

Approval Date: June 7, 1999

Indication:

NDA 20-946/S-001

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

JUN 7 1999

Dear Ms. Filipiak:

Please refer to your supplemental new drug application dated September 22, 1998, received September 23, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Preven™ Emergency Contraceptive Kit (levonorgestrel/ethinyl estradiol).

We acknowledge receipt of your submissions dated October 2 and 30, November 30, December 4, 1998 and May 18, 1999.

We have completed the review of this supplemental 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 agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted May 18, 1999).

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 supplement NDA 20-946/S-001." Approval of this submission by FDA is not required before the labeling is used.

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

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we

request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 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 Jennifer Mercier, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/ M.D. (for LRARICK)

Lisa D. Rarick, M.D. 6/7/99
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 20946/S001

MEDICAL REVIEW(S)

Medical Officer's Review / MAY 4 1999

NDA 20-946
Supplemental Labeling Request-001

Date Received: 9/23/98
Review Finalized: 4/28/99

Sponsor: Gynetics
Drug: Preven™

A. Sponsor's Request for Labeling Revisions.

The Sponsor seeks to remove the black box warning and the contraindication regarding heavy smoking and age over 35. The Sponsor supports its requests by discussing the following:

1. The clinical evidence supports that the risk of pregnancy is greater than the risk of use of Preven™ in a woman who is a smoker and over the age of 35.

Reviewer's Comment: The Sponsor (Gynetics) has not presented the clinical evidence that would support this statement. Indeed, I am not aware that the risk of taking the drug regimen in Preven™ has ever been studied in heavy smokers over the age of 35. Therefore, the risk of taking Preven™ in a smoker over the age of 35 is unknown.

2. The Federal Register Notice of February 25, 1997 states that experience with approved products in Europe and New Zealand has demonstrated the regimens to be safe.

3. The presentation at the June 28, 1996 FDA Advisory Committee for Reproductive Health of information from the British Medicines Control Agency revealed that only six serious adverse reactions associated with emergency contraceptive products were reported 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.

4. The Code of Federal Regulations, **21 CFR 201.57 (d)** describes contraindications as those situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit.

Reviewer's Comment: Because the risk of Preven™ use in women who smoke and are over the age of 35 are unknown and do not clearly outweigh any possible benefit, this would support the Sponsor's contention that should be removed as a Box Warning and Contraindication. However, a statement regarding the risk of oral contraceptive regimens (1 pill each day for 21 days of a 28-day cycle) in smokers over the age of 35 should be placed in the Warnings section. Therefore the following labeling recommendations are made:

CONTRAINDICATIONS

Redacted 5

pages of trade

secret and/or

confidential

commercial

information

/S/

Shelley R. Slaughter, M.D., Ph.D.
Medical Reviewer, DRUDP

/S/

Concurrence: Marianne Mann 5/4/99
Deputy Director, DRUDP

CC: NDA 20-946 Division Files
HFD580/L.Rarick/M.Mann/S.Slaughter/J. Mercier

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20946/S001

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-946/S-001

SEP 2 8 1998

Gynetics Inc.
56 Locust Lane
Princeton, NJ 08540

Attention: Margaret P. Filipiak

Dear Mrs. Filipiak:

We acknowledge receipt of your supplemental application for the following:

Name of Drug:	Preven (levonorgestrel/ ethinyl estradiol)
NDA Number:	20-946
Supplement Number:	S-001
Date of Supplement:	September 22, 1998
Date of Receipt:	September 23, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on November 22, 1998 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation II
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

TSI

for Lana L. 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 20-946/S-001
HFD-580/Div. Files
HFD-580/CSO/C. Kish

SUPPLEMENT ACKNOWLEDGEMENT

ORIGINAL

AJ 4/30/99

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

SUPPL NEW CORRESP

December 4, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH REC'D DEC 7 1998 HFD-580

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/Supplement # 002/ Priority Review Request for Labeling Supplement 001

On September 22, 1998, Gynétics Inc submitted the above-referenced supplement seeking Food and Drug Administration (FDA) approval to amend its labeling for its approved PREVEN™ Emergency Contraceptive Kit. Specifically, the supplement proposed removal, from the product's labeling, of certain warnings and contraindications concerning smoking, due to the infrequent and very short-term use of the product and consequent minimal risk of adverse effects from smoking. At the meeting of FDA Advisory Committee for Reproductive Health Drugs of June 28 1996, information from the British Medicine Control Agency was presented which showed that only six serious adverse reactions were reported. Of these, only one occurred close enough to the time of administration to indicate that the reaction might be drug related. The data demonstrate that these warnings and contraindications are based on chronic use, and are therefore not appropriate for PREVEN™. To date, Gynétics has not heard from the agency regarding the supplement. Given the importance of this product, Gynétics urges that the FDA review the supplement on a priority basis.

In February 1197, FDA published a Federal Register notice specifically inviting the submission of New Drug Applications (NDAs) for emergency contraception based on the agency's finding that "certain combined oral contraceptives containing ethinyl estradiol and norgestrel or levonorgestrel are safe and effective for use as postcoital emergency contraception." 62 Fed. Reg.8609, 8610 (Feb 25, 1997). Further, the agency dispensed with the need for sponsors of such NDAs to submit safety and effectiveness data, due to the public availability of such data, and instead permitted citations to references listed in the Federal Register notice to fulfill the data requirements.

See written review 4/30/99

4/30/99

Gynétics' NDA for PREVEN™ was submitted directly in response to FDA's call for such NDAs, and was granted priority review. Priority review is granted to applications and supplements for products that represent "a significant improvement, compared to marketed products [approved (if such is required), including non-"drug" products/ therapies] in the treatment, diagnosis, or prevention of a disease." CDER Manual of Policies and Procedures, 6020.3 (Priority Review Policy). "Evidence of increased effectiveness in treatment, prevention or diagnosis of disease," "elimination or substantial reduction of a treatment-limiting drug reaction," "documented enhancement of patient compliance," or "evidence of safety and effectiveness of a new subpopulation" are all ways of demonstrating a "significant improvement" over existing therapies. Id

In granting priority review of the original NDA, FDA recognized the substantial clinical advantages of PREVEN™ to the alternatives for emergency contraception. PREVEN™ currently represents the only approved specifically for this indication and dosage regimen. However, the warnings and contraindications regarding smoking have the effect of discouraging use of the product since they may overstate the actual dangers of using the product. A potential user may be deterred from using the product even though it is safer than other alternatives. Moreover, these warnings and contraindications limit the ways in which the product can be promoted. For example, reminder advertisements cannot be used when there is a blackbox warning. As explained in the supplement, these warnings are inappropriate in that they are tailored to patients who take regular birth control pills on a daily basis, as opposed to patients who use the pills for emergency contraception on an infrequent or rare basis.

In light of FDA's solicitation of NDAs for this specific drug product, the subsequent grant of priority review to Gynétics' NDA, the fact that PREVEN™ remains the only approved drug therapy for emergency contraception, and the importance of this product to public health, Gynétics requests that the agency review on a priority basis the company's NDA Supplement # 001 to amend the labeling of PREVEN™. Priority review is needed to effectuate the agency's objectives of allowing access to an FDA-approved version of this therapy. The current warnings and contraindications related to smoking are medically unnecessary and have a significant negative impact on patient access to this very important product both by discouraging women from using it and inhibiting informational activities. Priority review is therefore warranted.

Sincerely yours,

Margaret P. Filipiak
For Gynétics Inc.

Copy: Gynétics

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

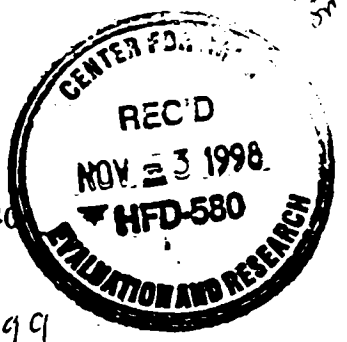
NDA 20-946 ORIGINAL

NEW CORRESP

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



October 30, 1998

Lisa Stockbridge, PhD
Division of Drug Marketing, Advertising and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane,
Rockville, MD 20857-1706

Dear Dr. Stockbridge,

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

On behalf of Gynétics, we herewith submit a pharmacy journal advertisement which will be published in November, a toll free number script for product information in Spanish, and several promotional letters which were inadvertently not submitted earlier.

The materials have been submitted in duplicate.

Yours sincerely,

Margaret P. Filipiak
For Gynétics Inc.

Enc. 2 binders of Promotional Materials, Copy of Cover letter to Division of Reproductive and Urologic Drug Products

Copy: Division of Reproductive and Urologic Drug Products
Gynétics Inc

1-14

ORIGINAL

Margaret P. Filipiak
Pharmaceutical Regulatory Affairs

Phone: 609 924 4808
Fax: 609 252 0469
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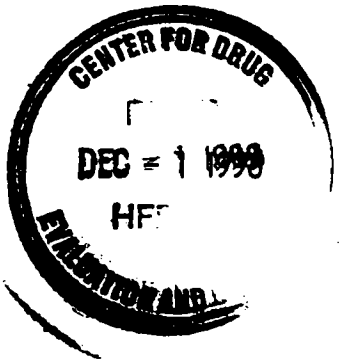
56, Locust Lane
Princeton, NJ 08540

November 30, 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/ FPL for approved NDA 20-946

Reference is also made to the September 18, 1998 submission of Final Printed Labeling. The Patient Information Book which was printed and submitted on September 18 had inadvertently been printed with some minor errors. These errors have been rectified and therefore we are resubmitting the Patient Information Book (PIB) piece of the FPL. We attach two copies of the previously submitted PIB which has the typographical errors highlighted for the convenience of the reviewer.

Ten copies of the PIB are mounted on heavy-weight paper. Twenty copies of the PIB in total are submitted.

Yours sincerely,

Margaret P. Filipiak

Margaret P. Filipiak
For Gynétics Inc.

Enc.: 356h Form
20 copies of FPL

Copy: Gynétics Inc

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS DATE

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

NDA NO. 20-946 REF. NO. 001
NDA SUPPL FOR SLR

September 22, 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/Supplement # 001/ Labeling

As you are aware, the labeling for the above drug product has been a source of ongoing discussion between Gynétics and the Division. Since the approval of the NDA, Gynétics has been meeting with legal and medical advisors to further discuss the package labeling. We have concluded that there is a need to amend the labeling to take into account that although the active ingredients are those of combination oral contraceptives (COCs), they will not be taken on a daily basis but rather on an infrequent basis.

The warnings, contraindications and, particularly, the black box warning regarding smoking are based on the chronic and prophylactic use of combination oral contraceptives (COCs). In contrast, the birth control pills in the PREVEN™ Emergency Contraceptive Kit are taken infrequently and possibly only once in a woman's lifetime. The woman contemplating the use of emergency contraceptive pills believes she is at risk of being pregnant. The woman who is a smoker and over 35 faces the relative risk of the pregnancy or the pills. Strong clinical evidence supports Gynétics opinion that the risk of pregnancy is more serious than taking the pills. As pointed out by the Division in the Federal Register Notice of February 25, 1996, experience with approved products in Europe and New Zealand has demonstrated the regimens to be safe. In addition, 21 CFR 201.57(d) describes contraindications as those situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit. Accordingly, the black box warning regarding smoking and the contraindication regarding smoking are inappropriate.

Review complete 4/30/99
See unsigned review

We therefore attach an amended Physicians' Insert (PI) and amended Detailed Patient Labeling (PPI) with the black box warning regarding smoking and the contraindication regarding smoking struck out. For the convenience of the reviewer, the aforementioned sections are blacklined. The pages that are amended are pages 7 and 12 of the PI, and page 2 of the PPI. This supplement is submitted in duplicate.

Yours sincerely,

Margaret P. Filipiak

Margaret P. Filipiak
For
Gynétics Inc.

Copy: Gynétics

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CS[illegible]IALS DATE

ORIGINAL

NDA SUPP AMEND

SLR 091 SL NDA NO. 20946 REF. NO. ~~SLR~~

NDA SUPPL FOR ~~DEVA~~

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

May 18, 1999

By Federal Express

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/Supplement # 004/ Draft Labeling

As discussed on the telephone today, we herewith submit the draft labeling with the changes that were faxed to the Division on May 14, 1999. The changes have been blacklined for the convenience of the reviewer.

This supplement is being submitted in duplicate (four copies).

Yours sincerely,

Margaret P. Filipiak

Margaret P. Filipiak
For
Gynétics Inc.

Copy: Gynétics

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