CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21045

CHEMISTRY REVIEW(S)

JUL 27 1999

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS - HFD-580

Review of Chemistry, Manufacturing and Controls

NDA #: 21-045
CHEMISTRY REVIEW #: 3
DATE REVIEWED: 27-JUL-1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	29-JAN-99	29-JAN-99	05-FEB-99
Amendment	23-JUL-99	23-JUL-99	
Amendment	27-JUL-99	27-JUL-99	

NAME & ADDRESS OF SPONSOR: Women's Capital Corporation
550 Kirkland Way
Suite 204
Kirkland, WA 98033

DRUG PRODUCT NAME:

Proprietary:	Plan B
Nonproprietary/Established/USAN:	Levonorgestrel Tablets
Code Name/#:	
Chem.Type/Ther.Class:	3P

PARMACOLOGICAL CATEGORY/INDICATION:	Progestin/Emergency contraceptive
DOSAGE FORM:	Tablet
STRENGTHS:	0.75 mg
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	___x___ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

a. 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17α)-(-)-
b. (-)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one
See Chem. Rev. #1 for the chemical structure and molecular formula.

CONCLUSIONS & RECOMMENDATIONS:
This NDA may be approved from a CMC point of view.

cc:
Orig. NDA #21-045
HFD-580/Division File
HFD-580/JMercier
HFD-580/MRhee/DLin

R/D Init by: 7/27/99
filename: nda21045.3 (doc)

/S/ 7/23/99
David T. Lin, Ph.D.
Review Chemist

SUPPORTING DOCUMENTS:
See Chem. Rev. #2.

RELATED DOCUMENTS:
none

PATENT STATUS:
See Chem. Rev. #1.

CONSULTS:

1. The EER was sent to Compliance on February 4, 1999. A final acceptable recommendation was received on July 27, 1999.

Also, see Chem. Rev. #1 and #2.

REMARKS/COMMENTS:
Plan B tablets contain as the active component, the progestin, levonorgestrel USP. Levonorgestrel is a well characterized progestin that is the active component in a number of approved contraceptive drug products. This NDA has been submitted for the use of oral 0.75 mg levonorgestrel tablets as an emergency contraceptive for occasional use after a contraceptive accident or unprotected sex.

The July 23, 1999 and July 27, 1999 submissions are final labeling amendments.

JUL 15 1999

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

NDA #: 21-045
CHEMISTRY REVIEW #: 2
DATE REVIEWED: 14-JUL-1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	29-JAN-99	29-JAN-99	05-FEB-99
Amendment	18-MAY-99	19-MAY-99	24-MAY-1999
Amendment	21-MAY-99	21-MAY-99	27-MAY-1999
Amendment	17-JUN-99	17-JUN-99	22-JUN-1999
Amendment	06-JUL-99	06-JUL-99	07-JUL-1999
Amendment	13-JUL-99	14-JUL-99	14-JUL-1999

NAME & ADDRESS OF SPONSOR: Women's Capital Corporation
550 Kirkland Way
Suite 204
Kirkland, WA 98033

DRUG PRODUCT NAME:
Proprietary: Plan B
Nonproprietary/Established/USAN: Levonorgestrel Tablets
Code Name/#:
Chem.Type/Ther.Class: 3P

PARMACOLOGICAL CATEGORY/INDICATION: Progestin/Emergency contraceptive
DOSAGE FORM: Tablet
STRENGTHS: 0.75 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
a. 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17α)-(-)-
b. (-)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one
See Chem. Rev. #1 for the chemical structure and molecular formula.

CONCLUSIONS & RECOMMENDATIONS:
This NDA is approvable pending a final review of the labeling and a satisfactory recommendation from Compliance.

cc:
Orig. NDA #21-045
HFD-580/Division File
HFD-580/JMercier
HFD-580/MRhee/DLin

R/D Init by: 7/14/99
filename: nda21045.2 (doc)

/S/ 7/14/99
David T. Lin, Ph.D.
Review Chemist

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
IND			Active	N/A	N/A
DMF			Adequate	5/7/99	N/A
DMF			Adequate	7/11/99	N/A
DMF			Adequate	10/29/97	N/A

RELATED DOCUMENTS:
none

PATENT STATUS:
See Chem. Rev. #1.

CONSULTS:

1. The Division of Biopharmaceutics has been consulted for the dissolution specifications. The sponsor has agreed to the recommended revised specifications of Q % at minutes.
2. The EER was sent to Compliance on February 4, 1999. Final recommendation has not been received.

REMARKS/COMMENTS:
Plan B tablets contain as the active component, the progestin, levonorgestrel USP. Levonorgestrel is a well characterized progestin that is the active component in a number of approved contraceptive drug products. This NDA has been submitted for the use of oral 0.75 mg levonorgestrel tablets as an emergency contraceptive for occasional use after a contraceptive accident or unprotected sex. The submitted stability data will only support an 8 month expiry date, and the sponsor has agreed to this recommendation.

The May 18, 1999 amendment is a partial response to the May 14, 1999 FDA information request letter.

The May 21, 1999 amendment contains the responses to Comments # 5, 10, and 11 in the May 14, 1999 FDA information request letter.

The June 17, 1999 amendment contains the responses to Comments # 1-4 and 10 in the May 14, 1999 FDA information request letter.

The July 6, 1999 amendment contains the 8 month stability data point for 3 drug product batches, the final methods validation package, and further clarification of bulk drug product storage conditions.

The July 13, 1999 amendment contains the revised dissolution specifications, information on the in-process controls for blistering, and acceptance of the FDA recommended 8 month expiry date.

D-1

MAY 13 1999

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS - HFD-580

Review of Chemistry, Manufacturing and Controls

NDA #: 21-045
CHEMISTRY REVIEW #: 1
DATE REVIEWED: 12-MAY-1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	29-JAN-99	29-JAN-99	05-FEB-99
Amendment	12-APR-99	11-MAY-99	
Amendment	28-APR-99	29-APR-99	30-APR-99
Amendment	29-APR-99	29-APR-99	30-APR-99

NAME & ADDRESS OF SPONSOR:

Women's Capital Corporation
550 Kirkland Way
Suite 204
Kirkland, WA 98033

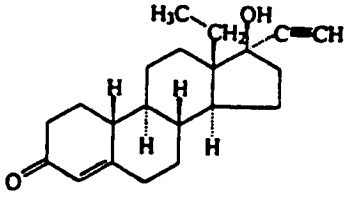
DRUG PRODUCT NAME:

Proprietary:	Plan B
Nonproprietary/Established/USAN:	Levonorgestrel
Code Name/#:	
Chem.Type/Ther.Class:	2P

PARMACOLOGICAL CATEGORY/INDICATION:	Progestin/Emergency contraceptive
DOSAGE FORM:	Tablet
STRENGTHS:	0.75 mg
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	x Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

a. 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17α)-(-)-
b. (-)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one



Molecular formula: $C_{21}H_{28}O_2$
Molecular weight: 312.45
CAS # 797-63-7

CONCLUSIONS & RECOMMENDATIONS:

This NDA is approvable pending satisfactory resolution of the issues delineated in the draft letter.

cc:
Orig. NDA #21-045
HFD-580/Division File
HFD-580/JMercier
HFD-580/MRhee/DLin

R/D Init by: 5/13/99
filename: nda21045.1 (doc)

/S/ 5/12/99
David T. Lin, Ph.D.
Review Chemist

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
IND			Active	N/A	N/A
DMF			Adequate	5/7/99	6/30/98
DMF			Pending		9/7/98
DMF			Adequate	10/29/97	11/24/98

RELATED DOCUMENTS:
none

PATENT STATUS:

Patent No.	Type	Expiration	Patent Owner
5,565,466	Method of Use	8/9/2014	Zonagen, Inc.
5,731,339	Formulation and Method of Use	4/28/2015	Zonagen, Inc.

CONSULTS:

1. The Division of Biopharmaceutics has been consulted for the dissolution specifications.
2. The EER was sent to Compliance on February 4, 1999.
3. The proposed trademark, Plan B, was consulted to the Nomenclature and Labeling Committee. The Committee determined the tradename to be unacceptable (September 3, 1998; see appendix A). Further discussion of the trademark can be found in the labeling section of this review.

REMARKS/COMMENTS:
Plan B tablets contain as the active component, the progestin, levonorgestrel USP. Levonorgestrel is a well characterized progestin that is the active component in a number of approved contraceptive drug products. This NDA has been submitted for the use of oral 0.75 mg levonorgestrel tablets as an emergency contraceptive for occasional use after a contraceptive accident or unprotected sex. The same formulation tablets are currently marketed as Postinor in ten-tablet and four-tablet packages in 34 countries, including all of Eastern Europe and the former Soviet Union.

The April 28, 1999 amendment contains a corrected dissolution report.

The April 12 and April 29, 1999 amendments contain updated stability data.