CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-683

CHEMISTRY REVIEW(S)

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS HFD-580

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-683 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 24-MAR-97 **REVISED:** 25-MAR-95

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original NDA N-000	27-MAR-96	27-MAR-96	05-APR-96
BC	30-JAN-97	03-FEB-97	06-FEB-97
BC	14-FEB-97	18-FEB-97	19-FEB-97
BC	12-MAR-97	13-MAR-97	13-MAR-97
BC	24-MAR-97	25-MAR-97	25-MAR-97

NAME & ADDRESS OF APPLICANT: Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia, PA 19101-8299

DRUG PRODUCT NAME

Proprietary:	Alesse™
Nonproprietary/USAN:	Levonorgestrel/ethinyl estradiol
Code Name/#:	3010600
Chem.Type/Ther.Class:	3S

PATENT STATUS: Not under patent

PHARMACOL.CATEGORY/INDICATION: Prevention of pregnancy in women

DOSAGE FORM: tablet

STRENGTHS:

levonorgestrel	0.100 mg
ethinyl estradiol	0.020 mg

ROUTE OF ADMINISTRATION: oral

DISPENSED: X Rx _ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

See Review # 1

SUPPORTING DOCUMENTS: None

CONSULTS: Biopharmaceutics

REMARKS/COMMENTS:

This NDA is for a low dose formulation oral contraceptive with levonorgestrel as the progestational component and ethinyl estradiol as the estrogenic ingredient. The sponsor plans to market this combination in both standard 21-day and 28-day (7 days of placebo) regimens. This review is of responses to information requests by telephone and in a January 30, 1997 Agency letter in regard to the chemistry, manufacturing and controls of the drug.

CONCLUSIONS & RECOMMENDATIONS:

This new drug application is may be approved in regard to chemistry. The approval letter should state that the fourteen batches already manufactured with a [redacted]% overage can be released since their batch release data have been reviewed by FDA and found to be acceptable.

cc:
Orig. NDA 20-683
HFD-580/Division File
HFD-580/Chemist/Seevers
HFD-580/CSO/Kish
R/D Init by: Rhee 3/25/97

Robert H. Seevers, Chemist

K15/7

JAN 27 1997

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS HFD-580

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-683 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 16-JAN-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original NDA N-000	27-MAR-96	27-MAR-96	05-APR-96

NAME & ADDRESS OF APPLICANT: Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia, PA 19101-8299

DRUG PRODUCT NAME

Proprietary:	Alesse™
Nonproprietary/USAN:	Levonorgestrel/ethinyl estradiol
Code Name/#:	3010600
Chem.Type/Ther.Class:	3S

PATENT STATUS: Not under patent [1.1:4]

PHARMACOL.CATEGORY/INDICATION: Prevention of pregnancy in women

DOSAGE FORM: tablet

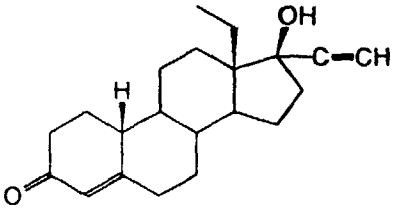
STRENGTHS:

levonorgestrel	0.100 mg
ethinyl estradiol	0.020 mg

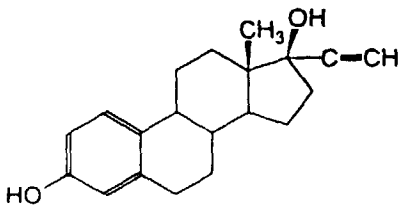
ROUTE OF ADMINISTRATION: oral

DISPENSED: X Rx _ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:



Levonorgestrel
(-)-13-ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one
$C_{21}H_{28}O_2$
M.W. = 312.45



Ethinyl estradiol
19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol
$C_{20}H_{24}O_2$
M.W. = 296.41

SUPPORTING DOCUMENTS:

DMF #	Holder	Item
		Ethinyl Estradiol, USP
		Levonorgestrel, USP
		Mini-Pack Unit
		Mini-Pack Unit

CONSULTS:

A request for inspection of the drug substance manufacturing sites in was forwarded to Compliance May 7, 1996. They were deemed Acceptable on May 23, 1996.

A request for evaluation of the trademark Alesse™, was sent to the Labeling and Nomenclature Committee on May 7, 1996. The LNC found the trademark acceptable on June 20, 1996.

A Finding of no Significant Impact was prepared and submitted to the Environmental Assessment staff. It was signed off by Nancy Sager for the Environmental Assessment Team on January 7, 1997.

REMARKS/COMMENTS:

This NDA is for a low dose formulation oral contraceptive with levonorgestrel as the progestational component and ethinyl estradiol as the estrogenic ingredient. The sponsor plans to market this combination in both standard 21-day and 28-day (7 days of placebo) regimens.

CONCLUSIONS & RECOMMENDATIONS:

This new drug application is approvable from a chemistry standpoint subject to the following provisions:

Drug Product Manufacture

The firm should be asked to provide either documentation of manufacturing losses to justify the % overage in the formulation submitted for the drug product, or to revise the formulation of the active tablet to reduce or eliminate the overage based on the actual manufacturing data submitted.

The firm needs to provide information on the storage of the levonorgestrel and estradiol triturations before use and on the storage of the tablet cores before coating including descriptions of the container/closure systems used, the environmental conditions of storage (i.e. temperature and humidity) and any limits placed on the length of storage before use of the

The firm needs to submit specifications for the in-process controls and tests. The present submission provides only the actual specifications of the tests in the Master Batch Record and reserves the right to modify the Master Batch Record "within the context of the regulatory method of manufacture."

The sponsor needs to state whether reprocessing operations are proposed for material in the manufacturing process that deviates from specifications. If reprocessing is proposed, then it will need to submit a brief summary of the proposed reprocessing procedures as well as information about maximum holding times and storage conditions before reprocessing and any additional controls used.

A deficiency letter has been sent to holder of DMF for the Mini-Pack™ units used to package the drug product. However, there is a second supplier of the Mini-Packs units, , whose DMF was adequate to support the application.

Labeling

Since the placebo pills in the 28 day formulation have been shown to fade on exposure to light, the sponsor should revise the Dosage and Administration section of the prescribing information labeling to include the following:

Similarly the section, How to Use the Alesse Mini-Pack in the Detailed Patient Labeling should be revised to include the following:

Storage During Clinical Trials

Since the sponsor has found that a small amount of migrates from the wallets to the active and placebo pills in opened Mini-Packs stored in the wallets, a concern over the effect of this on the bioavailability of the drug substances has been raised. The sponsor has been queried as to whether the wallets

were used by the subjects in the clinical trials to store the opened Mini-Packs and they have promised an answer in the near future. If the wallets were used then any bioavailability concerns are moot. If not, then this issue will have to be referred to the Biopharmaceutics reviewer.

cc:
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R/D Init by: Rhee 1/27/97

Robert H. Seevers, Chemist