CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-276

CHEMISTRY REVIEW(S)

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-276 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 11/15/00

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	30-Jun-2000	03-Jul-2000	08-Aug-2000

NAME & ADDRESS OF APPLICANT: Parke-Davis Pharmaceutical Research,
Division of Warner-Lambert
2800 Plymouth Road
Ann Arbor, Michigan 48106-1047

DRUG PRODUCT NAME

Proprietary:	Estrostep
Nonproprietary/USAN:	ethinyl estradiol (EE) and norethindrone acetate (NA)
Code Names/#'s:	not specified
Chem.Type/Ther.Class:	6 S

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

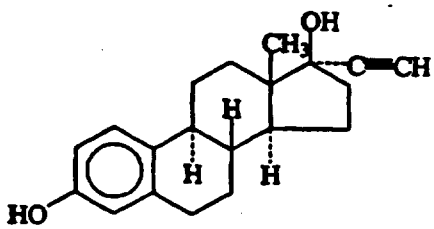
PHARMACOL.CATEGORY/INDICATION: moderate acne vulgaris

DOSAGE FORM: Tablets
STRENGTHS: 1 mg NA/20 μg EE;
1 mg NA/30 μg EE;
1 mg NA/35 μg EE

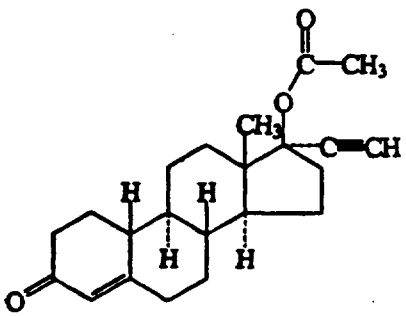
ROUTE OF ADMINISTRATION: Oral
DISPENSED: _x_ Rx __ OTC

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

ethinyl estradiol
$C_{20}H_{24}O_2$
MW=296.41



norethindrone acetate
$C_{22}H_{28}O_3$
MW=340.46



SUPPORTING DOCUMENTS:

NDA 21-065	Parke-Davis	Femhrt (Ethinyl Estradiol/ Norethindrone A) OC
NDA 17-354	Parke-Davis	Loestrin-Fe (Ethinyl Estradiol/ Norethindrone Ferrous) OC
NDA 17-355	Parke-Davis	Loestrin (Ethinyl Estradiol/ Norethindrone Acetate) OC
NDA 17-875	Parke-Davis	Loestrin 21 (Ethinyl Estradiol/ Norethindrone Acetate) OC
NDA 17-876	Parke-Davis	Loestrin 20 (Ethinyl Estradiol/ Norethindrone Acetate) OC

Footnote: Deficiency letters were issued on 9/14/00 and 9/13/00 for [redacted] because

it failed to include adequate information regarding [redacted] This DMF was also inadequate because it was not correctly paginated. Although deficiency letters were issued to the DMF holder for [redacted] it does not affect the subject NDA (NDA 21-276) because a different [redacted] was used in this NDA and is the packaging component of a marketed product. However, the DMF holder should be notified by information request letter to indicate where the information of the [redacted] is located in the DMF.

RELATED DOCUMENTS (if applicable):

[redacted]

NDA 20-130 Parke-Davis Estrostep21/ Estrostep Fe (Ethinyl Estradiol/ Norethindrone Acetate) OC

CONSULTS: None

REMARKS/COMMENTS:

The applicant filed an NDA in accordance with 21 CFR 314.50, 21 CFR 314.54 and agreements made during a pre-NDA meeting of 1/6/00. This NDA is the subject of a marketed product, Estrostep21/ Estrostep Fe (NDA 19-697) and is being submitted as a new indication to the presently approved product. The NDA only contains Clinical and Statistical Data in support of the application.

During the pre-NDA meeting of 1/6/00, the applicant was requested to submit a statement that the Chemistry, Manufacturing and Controls information for the two (2) drug substances and the drug product are the same as described in NDA 20-130 and that there have been no changes since the approval of the NDA on 10/8/00. The applicant indicated that have been no CMC changes; the CMCs are the same as submitted in NDA 20-130 (see Vol .1.3; pages 148 & 149). In this regard, the applicant cross-referenced NDA 20-130 for information relating to chemistry, manufacturing, and controls used in that NDA. Note: The CMCs were found approvable for NDA 20-130 [see Chemist Review #5 (HFD-580) dated 10/7/96].

The applicant was also requested to submit other CMC information as discussed during the pre-NDA meeting of 1/6/00. This information was submitted in vol. 1.3, page 148 and found acceptable. The applicant did not indicate any DMFs that were affected by CMC changes.

Environmental Assessment: Acceptable

A type 6 NDA for Estrostep (Ethinyl Estradiol/ Norethindrone Acetate) requires an Environmental Assessment in accordance with regulation 21 CFR Part 25.22 (a)(14). In this regard, the applicant requested a Categorical Exclusion from the Environmental Assessments under 21 CFR 25.31 (b) for this product based on information that was submitted as follows:

The active ingredients, norethindrone (NA) acetate and ethinyl estradiol (EE), are a well known ingredients used in commercial marketed products. The applicant indicated that these active ingredients are present in the their commercial marketed products, Estrostep tablets (NDA 20-130), Loestrin tablets and Femhrt tablets. The estimated concentration of both NA and EE at the point of entry into the aquatic environment is less than 1 part per billion (see calculations as submitted in Vol. 1.3, p. 153).

Since the EIC value for norethindrone (NA) acetate and ethinyl estradiol (EE) drug substance represents a level well below 1 ppb for the EIC, a claim for categorical exclusion has been requested.

Establishment Evaluation Review: Requested: 7/27/00
Overall Recommendation: Acceptable for GMPs
Office of Compliance: M. Garcia
Date: 9/5/00

Warner-Lambert Company
182 & 201 Tabor Rd
Morris Plains, NJ 07950

Responsibilities: Finished Dosage Stability Tester

OC Recommendation: 7/27/00 Acceptable based on profile

EERs were requested on 7/27/00 for the following facilities:

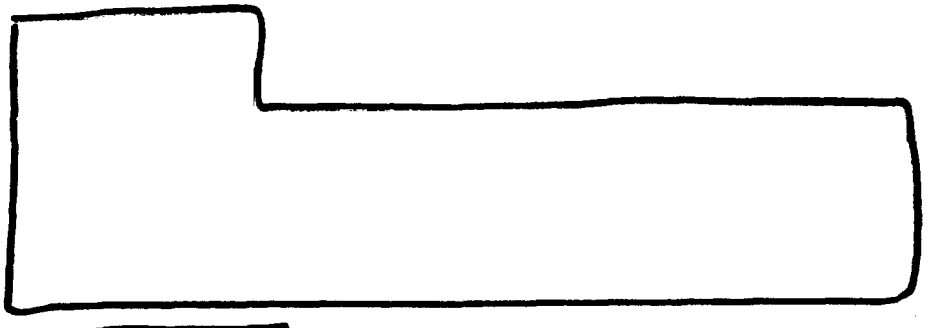
(1) Parke-Davis Pharmaceutical Research
Division of Warner-Lambert
2800 Plymouth Rd
Ann Arbor, MI 48106

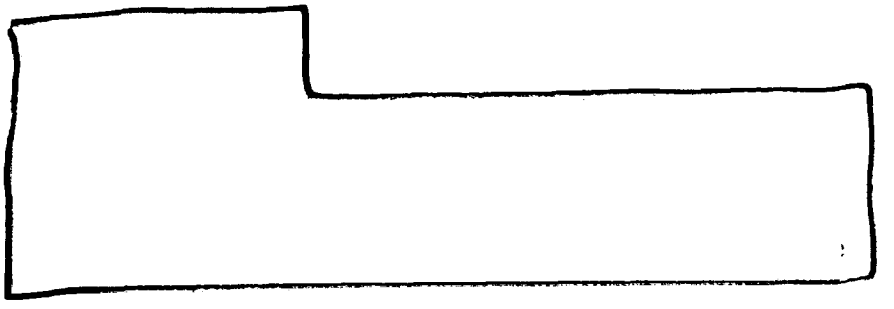
Responsibilities: Corporate Headquarters

(2) Parke-Davis Div Warner Lambert
KM 19 RD 689
Vega Baja, PR 00763

Responsibilities: Finisher Dosage Other Tester

OC Recommendation 7/27/00 Acceptable based on profile

(3) 

(4) 

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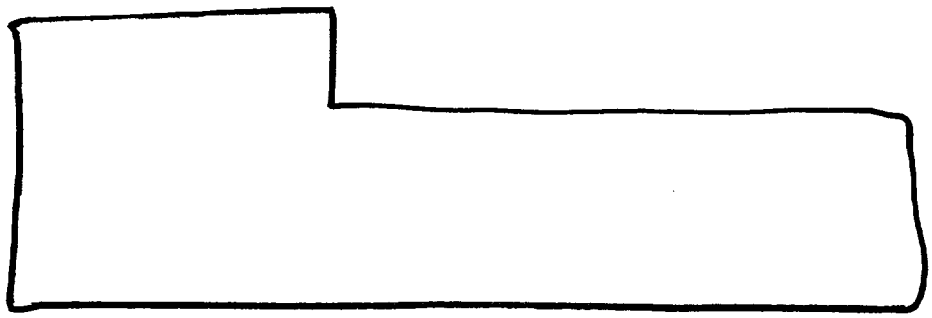

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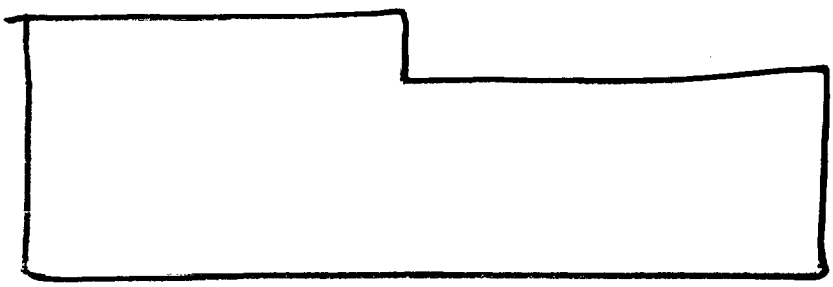

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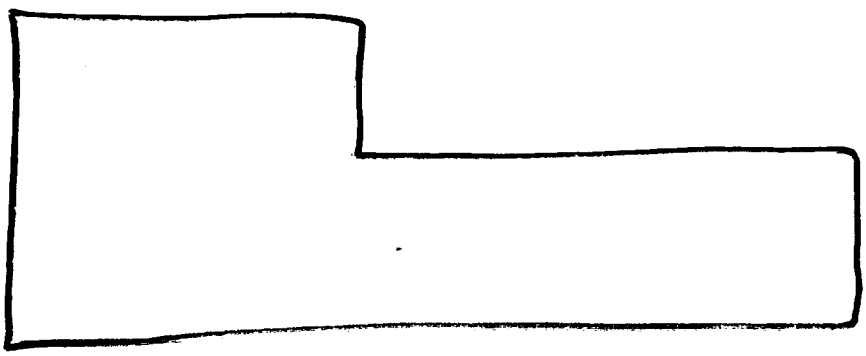

Labeling: Acceptable

Review of the labeling was not required from a technical standpoint because the drug product is a commercial available product for Estrostep tablets.

Since Estrostep is a commercial available product, OPDRA did not request the packaging labeling. Therefore, no consult was required for the subject NDA (see attached e-mail dated 9/18/00). OPDRA requested to see the labeling only if the applicant changes the tradename.

CONCLUSIONS & RECOMMENDATIONS:

The NDA is recommended for approval for manufacturing and controls under section 505 of the Act.

Ernest G. Pappas, Review Chemist

cc: Orig. NDA 21-276
HFD-540/Division File
HFD-540/Chem., Pappas
HFD-540/ MO, Porres
HFD-540/Pharm, Nostrandt
HFD-540/ CSO, Cintron
HFD-540/Chem.Team Leader, DeCamp