CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-276

ADMINISTRATIVE DOCUMENTS

ITEM 13
PATENT AND MARKET EXCLUSIVITY INFORMATION

This section of the NDA provides patent information required under Section 21 U.S.C. 355(b)(1) and documents the market exclusivity period applicable to Estrostep®.

13.1. Patent Information

NDA Number:	21-276
Original NDA number for Oral Contraceptive Indication	20-130
Applicant:	Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company 2800 Plymouth Road Ann Arbor, MI 48106
Active Ingredient:	Norethindrone acetate (NA) and ethinyl estradiol (EE)
Medical Use:	Oral contraceptive and for the treatment of moderate acne vulgaris
Strength:	Estrostep® is a combined, graduated estrogen oral contraceptive (OC) consisting of constant dose of the synthetic steroids NA and increasing dose of EE 5 days—1 mg NA/20 µg EE 7 days—1 mg NA/30 µg EE 9 days—1 mg NA/35 µg EE
Dosage Form:	Tablet
Trade Name:	Estrostep®

Generic Name:	Norethindrone acetate/ethinyl estradiol tablets USP	
Patent Statement:	Two patents covers oral contraception	
A.	US Patent Number:	4, 962,098
	Expiration Date:	October 9, 2007
	Patent Type	Method of use
	Assignee:	Warner-Lambert Company
B.	US Patent Number:	5,010,070
	Expiration Date:	April 23, 2008
	Patent Type	Combination package
	Assignee:	Warner-Lambert Company
Exclusivity	3 years from date of NDA approval	

The undersigned declares that Patent No. 4,962,098 covers the contraceptive use of Estrostep, and that Patent No. 5,010,070 covers the multiphase combination and contraceptive kit of Estrostep as approved in NDA 20-130, and is the subject of this NDA 21-276 submitted under Section 505 of the Federal Food, Drug and Cosmetics Act for which approval is sought.

Charles W. Ashbrook
Assistant General Counsel, Pharmaceutical Patents
Warner-Lambert Company

13.2. Request for Market Exclusivity

Estrostep tablets qualify for 3 years exclusivity. Warner-Lambert Company certifies that the active moieties (norethindrone acetate and ethinyl estradiol) of Estrostep tablets meet the criteria for the exclusivity period specified in 21 U.S.C. 355(j)(4)(D)(iii) and 355(c)(3)(D)(iii), specifically:

1. No drug product containing the same strengths of active ingredients, norethindrone acetate and ethinyl estradiol, in combination have been previously approved for the indication for which approval is sought in this application. (*Treatment of moderate acne vulgaris in females between 14 and 49 years of age, who have no known contraindication to oral contraceptive therapy, desire contraception, have achieved menarche, and are unresponsive to topical anti-acne medications.*). The combination of active ingredients, NA and EE, has been previously approved, for the use as an oral contraceptive.

2a. Two new clinical investigations, other than bioavailability or bioequivalence studies, are submitted to support this application. Warner-Lambert certified that to the best of applicant's knowledge, these clinical studies have not formed part of the basis of a finding of substantial evidence of effectiveness for a previously approved new drug application.

2b. The new clinical investigations can be found in Item 8 of the application, NDA 21-276, filed concurrently herewith.

3a. Within Item 8 of the application, NDA 21-276, filed concurrently herewith, list all published studies and publicly available reports of clinical investigations known to the applicant that are relevant to support the application.

3b. Warner-Lambert certifies that applicant has thoroughly searched the scientific literature and that the list of published studies and publicly available reports is complete and accurate.

3c. Warner-Lambert certifies that, in applicant's opinion, the present application could not have been approved without the new clinical investigations. The published

studies noted in 3a above are not sufficient to support the approval of the application.

4. Warner-Lambert Company is the sponsor named in the Form FDA 1571 for [redacted] under which the clinical investigations identified in 2a above was performed.

Exclusivity Summary Form

EXCLUSIVITY SUMMARY FOR NDA # 21-276 HFD-540
SUPPL #_____

Trade Name: Estrostep Tabs.

Generic Name: norethindrone acetate/ethinyl estradiol

Applicant Name: Pfizer (Parke Davis Pharmaceutical Research)

Approval Date If Known:_____

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 question about the submission.

a) Is it an original NDA?

YES/___/ NO /_X__/

b) Is it an effectiveness supplement?

YES /_X__/ 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 /_X__/ NO /___/

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.

_N/A_____

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:

_N/A_____

_____

d) Did the applicant request exclusivity?

YES /_X__/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety? **No**

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? (Rx to OTC switches should be answered NO - please indicate as such)

YES /___/ NO /_X__/

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 /_X__/

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 /___/ N/A

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 /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# REFER TO ATTACHMENT 1

NDA# ___20-130_____

NDA# _____

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 /_X__/ 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.

(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 /_X__/ 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 /_X__/ Note: Cannot identify section within the application that ~~would refer to the~~ safety and efficacy of the drug product.

(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 /_X__/

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 /___/ NA

If yes, explain:

(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: 376-403

Investigation #2: 376-404

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

(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 /_X__/ 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 /_X__/

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 /___/ NA

If yes, explain:

(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: 376-403

Investigation #2: 376-404

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 /_X_/

Investigation #2 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

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 /_X__/

Investigation #2 YES /___/ NO /_X__/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

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 #1: **376-403**

Investigation #2: **376-404**

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 # [redacted] YES /_X__/ NO /___/ Explain: _____

Investigation #2

IND # [redacted] YES /_X__/ 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? N/A

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 /_X__/

If yes, explain: _____

_____

Signature:Date:Title: /S/ 4/24/01.

Signature of Office/Division Director: /S/

Signature:Date: 6/29/01

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: N 021276
Trade Name: ESTROSTEP(ETHINYL ESTRADIOL/NORETHINDRO
Generic Name: ETHINYL ESTRADIOL/NORETHINDRONE ACETATE
Supplement Number. 000 **Supplement Type:** N
Dosage Form:
Regulatory Action: OP **Action Date:** 7/3/01

COMIS Indication: TREATMENT OF MODERATE ACNE VULGARIS

Indication #1: For the treatment of moderate acne vulgaris in females, ≥15 years of age, who have no known contraindications to oral contraceptive therapy, desire contraception, have achieved menarche, and are unresponsive to topical anti-acne medications.

Label Adequacy: Adequate for some pediatric age groups

Formulation Needed: Other

Comments:
Estrostep is an approved drug indicated for oral contraception. This new drug application provides for the treatment of moderate acne vulgaris in females, ≥15 years of age, who have no known contraindications to oral contraceptive therapy, desire contraception, have achieved menarche, and are unresponsive to topical anti-acne medications.

Lower Range	Upper Range	Status	Date
0 years	15 years	Waived	N/A

Comments:
Applicant requested a partial waiver to study Estrostep in females <14 years of age for the treatment of moderate acne vulgaris because: 1) moderate acne vulgaris is uncommon in females <14, and 2) oral contraceptives are not indicated for women prior to menses due to theoretic concerns over the premature advancement of bone age and its impact on final adult height. FDA is granting a partial waiver to the Applicant from conducting acne studies with Estrostep in female patients <15 years of age.

This page was last edited on 5/2/01

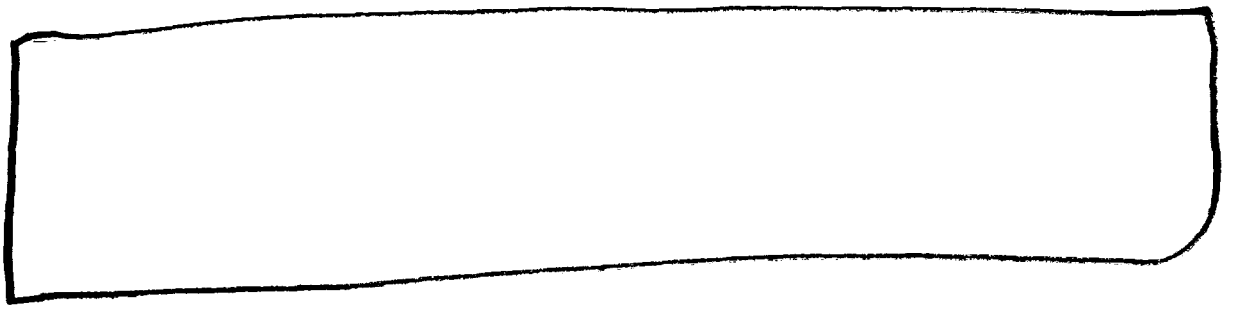
/S/ 5/2/01.
Signature Date

/S/ 5/2/01

/S/ 6/28/01

ITEM 16.
DEBARMENT CERTIFICATION

Warner-Lambert company hereby certifies that it is not debarred, and did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



XVIII. PEDIATRIC WAIVER.

SPONSOR'S REQUEST FOR PARTIAL PEDIATRIC WAIVER FOR COLLECTION OF SAFETY, EFFICACY, AND FOR PHARMACOKINETIC DATA OF ESTROSTEP® IN FEMALES · YEARS OF AGE

Sponsor is requesting a partial waiver from the study of Estrostep in females <14 years of age for the treatment of moderate acne vulgaris because; (1) moderate acne vulgaris is uncommon in females <14, and (2) oral contraceptives are not indicated for women prior to menses due to theoretic concerns over the premature advancement of bone age and its impact on final adult height. OCPs have generally been studied in women 18 and older and some studies have included girls as young as 15. In practice, OCPs are considered safe for girls younger than 16, as long as they are already menstruating

The mean age of menarche is 12.16 ± 2 years. The concern about treating younger girls with OCPs is based on the theoretic possibility of advancing their bone age prematurely prior to completion of their pubertal "growth spurt." The adolescent "growth spurt" in girls begins at a mean age of 9.6 years. At a mean age of 12.2 years, a girl begins menses, and she will have attained nearly 97% of her final adult height. Following menses, there is a slow, gradual increase in height until final adult height is achieved by approximately age 18.

Sponsor set the age cut-off for the acne studies at 14. There were few subjects exposed to Estrostep® younger than 18, an age where pharmacokinetics of ethinyl estradiol and norethindrone had not been previously determined. Sponsor conducted such studies in a few subjects within that age group and plans no other studies at this time. Estrostep is unlikely to offer a therapeutic benefit to females <14 years of age in treatment of acne and its use in this pediatric age group could pose theoretic risks regarding bone growth. Therefore, we request a waiver for collection of safety, efficacy and pharmacokinetic data in females <14 years of age.

> *Reviewer comment: since the drug would be approved only for use in females 15 or older, who have started to menstruate, want contraception with an oral contraceptive, can tolerate such oral contraceptive, plan to be on it for at least 6 months, and have moderate acne which has not responded to topical anti-acne medications, this reviewers considers a partial waver can be granted to the sponsor from having to Collect Safety, Efficacy, and Pharmacokinetic Data of Estrostep® in Females <15 Years of Age*

Medical review

Clinical Consultation

OCT 27 2000

FROM: Patricia Beaston-Wimmer, M.D., Ph.D.
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products

THROUGH: David Orloff, MD Director, DMEDP DG 10-27-00

TO: Olga Cintron, Project Manager, DDDDP

SUBJECT: The use of Estrostep (norethindrone acetate/ethinyl estradiol) for treatment of acne. NDA 21-276.

DATE CONSULT RECEIVED: September 13, 2000

DATE CONSULT COMPLETED: October 27, 2000

Material Received for Review

The consultation package included two Phase 3 study protocols for the pivotal studies included in the NDA, cover letter of the original submission, and the request for consultation form with specific questions.

Administrative Background

The Division of Dermatological and Dental Drug Products is requesting comment on a supplemental NDA providing a new indication to the approved Estrostep Tabs. This indication is for the treatment of acne vulgaris in females between [redacted] and 49 years of age.

Estrostep was approved for oral contraception in females on October 9, 1996. There was no age limitation listed in the label available to this reviewer.
Estrostep is a product of Parke-Davis, A Division of Warner Lambert

Ortho Tri-Cyclen (norgestimate/ethinyl estradiol), a product of Ortho-McNeil, received approval for the treatment of acne vulgaris in females, ≥ 15 years of age, who have no known contraindications to oral contraceptive therapy, desire contraception, have achieved menarche and are unresponsive to topical anti-acne medications.

Summary of Studies Provided

The studies were Protocol 376-403 and Protocol 376-404. Both studies were 6 month, double blind, placebo-controlled trials. The subjects were healthy females, aged [redacted] to 49

years who were ≥ 1 year post menarche with a baseline menstrual cycle of ≤ 42 days, had moderate facial acne, and had not responded adequately to topical antiacne therapy. A summary of the ages of patients enrolled in the studies is in the following table:

	Protocol 376-403			Protocol 376-404		
Age (years)	Placebo N = 148	Estrostep N = 150	Total N = 298	Placebo N = 147	Estrostep N = 146	Total N = 293
14*-15	22 (15%)	21(14%)	43(14%)	23(16%)	17(12%)	40(14%)
16-17	12 (8%)	13(9%)	25(8%)	10(7%)	18(12%)	28(10%)
18-21	32 (22%)	21(14%)	53(18%)	30(20%)	30(21%)	60(20%)
22-29	45 (30%)	51(34%)	96(32%)	52(35%)	59(40%)	111(38%)
30-39	31 (21%)	39(26%)	70(23%)	28(19%)	16(11%)	44(15%)
40-49	6 (4%)	5(3%)	11(4%)	4(3%)	6(4%)	10(3%)

*2 subjects were 13 years old in Protocol 376-403

Most Frequently Reported (>5%) Adverse Events by Age: Studies 376-403 and 376-404

Adverse events NDA 21-276 Table 5	Placebo N = 296				Estrostep N = 297			
	13-17 years		18-49 years		13-17 years		18-49 years	
	All	Assoc	All	Assoc	All	Assoc	All	Assoc
Metorrhagia	2 (3%)	2 (3%)	6 (3%)	5 (2%)	11 (16%)	11 (16%)	42 (18%)	40 (18%)
Infection	6 (9%)	0	32 (14%)	0	12 (17%)	0%	32 (14%)	0
Nausea	0	0	9 (4%)	6 (3%)	1 (1%)	1 (1%)	18 (8%)	15 (7%)
Flu Syndrome	4 (6%)	0	12 (5%)	0	3 (4%)	0	17 (7%)	0
Headache	12 (18%)	7 (10%)	16 (7%)	7 (3%)	4 (6%)	1 (1%)	16 (7%)	10 (4%)
Abdominal Pain	1 (1%)	0	2 (1%)	0	5 (7%)	1 (1%)	7 (3%)	4 (2%)
Pharyngitis	6 (9%)	0	12 (5%)	0	4 (6%)	0	6 (3%)	0
Accidental injury	1 (1	0	8 (3%)	0	3 (4%)	0	12 (5%)	0

The adverse events reported were no higher in the 13-17 year old group than the 18-49 year old group.

Requested Input

1) Possibility that women might develop premature bone closure from these hormones?

Historically, the safety and efficacy of oral contraceptives have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 years and for users 16 years and older. On review of the literature, no studies were found that specifically addressed the effects of oral contraceptives on the stature of adolescents. There are numerous studies addressing the use of estrogen in Turner's patients who are

hypogonadal. In this treatment the dose must be carefully balanced to promote growth without causing premature epiphyseal closure allowing the patient to achieve an increase in height. There are also a number of studies examining the use of estrogens to accelerate epiphyseal closure in girls with 'constitutional tall stature' to decrease their final height. In these cases, pharmacological doses of estrogen are used.

In general, premature epiphyseal closure should not be a concern in females who are one-year post menarche. The majority of growth occurs prior to menarche. In the first year after menarche, the increase in height averages 4 cm (range 2 to 6 cm) and after that an additional gain of 1.5 cm (range 0.5-3 cm) may occur. Much of this growth is in the axial skeleton.[1] Therefore, if treatment is started at one-year post menarche there may be small to modest effects on final height. The possibility that use of Estrostep prior to this point may reduce final height should obviously be weighed against the need for contraception (and treatment of acne).

In the event Estrostep is given consideration as a primary therapy for the treatment of acne vulgaris, it would be prudent to consider recommending that all patients less than two years post menarche have a bone age assessment prior to treatment. To minimize the potential for reduction in final height, the bone age should be at least 15 years.

The potential effects of estrogens on final height of adolescent females was not, to the best of my knowledge, specifically addressed in the review of Ortho Tri-Cyclen for the treatment of acne. The youngest patients enrolled in these studies were reported to be 15 years of age. There is no discussion regarding the criterion used for choosing the lower age limit for these studies.

2) Additional concerns with women using these kinds of hormones at this age and above.

In women of any age, signs of hyperandrogenism (hirsuitism in the appropriate races, severe acne, clitoromegaly, deepened voice) should be further evaluated for possibly pathology (e.g. adrenal hypertrophy). Both contraindications for the use of Estrostep and subsequent monitoring are addressed in the current label.

The use of oral contraceptives for the treatment of acne was addressed by HFD-580 for the supplement approval of Ortho Tri-Cyclen. A primary indication for this product for the treatment of acne was not approved. Discussions with HFD-580 are strongly encouraged regarding the approval of Estrostep for the treatment of acne. The Division of Metabolic and Endocrine Drugs would be happy to discuss this issue further with you and HFD-580, if so desired.

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[1] Tanner, J., In: Wilkins: The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, Fourth Edition (1994) pages 147-8, Editors: Kappy, M.S., Blizzard, R.M. and Migeon, C.J. Charles C. Thomas, Publisher

/S/
Patricia Beaston-Wimmer, M.D., Ph.D.
Medical Officer, DMEDEP

/S/ 10-27-09
David Orloff, MD Director, DMEDP

MEMORANDUM

Date: January 22, 2001

From: Brenda S. Gierhart, MD
Medical Officer, HFD-580

Through: Dena Hixon, MD
Team Leader, HFD-580

To: Olga Cintron, DDDDP, HFD-540

Subject: NDA 20-130 and NDA 21-276; Estrostep® Tablets (norethindrone acetate/ethinyl estradiol); Parke-Davis
Request for consultation (Tracked Correspondence #59) re: potential premature epiphyseal closure in postmenarcheal adolescents taking oral contraceptives

Date Assigned: December 6, 2000

Date Required: January 4, 2001

This replies to your request for consultation.

MATERIALS REVIEWED

1) **Clinical Consultation** from Patricia Beaston-Wimmer, MD, PhD from the Division of Metabolic and Endocrine Drug Products (DMEDP or HFD-510) dated October 27, 2000.

2) **NDA 20-130 Labeling Supplement 007** Volumes 1-3, which included 16 references

3) **PubMed search** performed by me on December 24, 2000.

4) **Review of additional references** (see-attached list).

DESCRIPTION OF THE SITUATION

The Division of Reproductive and Urologic Drug Products (DRUDP or HFD-580) approved NDA 20-130 Estrostep® Tablets (norethindrone acetate/ethinyl estradiol) by Parke-Davis as an oral contraceptive on October 9, 1996. On November 17, 2000, Parke-Davis submitted to NDA 20-130 the Labeling Supplement 007 for the use of Estrostep® in the treatment of moderate acne vulgaris. The Labeling Supplement 007 referenced the pending efficacy supplement NDA 21-276. NDA 21-276 was submitted by Parke-Davis to the Division of Dermatologic and Dental Drug Products (DDDDP or HFD-540) for the use of Estrostep® in the treatment of moderate acne vulgaris on June 30, 2000.

The current submission is a consultation request from DDDDP (HFD-540) to DRUDP (HFD-580) regarding a clinical consultation completed by Patricia Beaston-Wimmer, MD, PhD from the Division of Metabolic and Endocrine Drug Products (DMEDP or HFD-510) on October 27, 2000. The issue raised in the consult was whether postmenarcheal adolescents might develop premature epiphyseal closure from taking Estrostep® oral contraceptive pills. Dr. Beaston-Wimmer's consultation states that during her review of the literature, no studies were found that specifically addressed the effects of oral contraceptives on the stature of adolescents. The available literature seems limited to very different uses of estrogen, for example in Turner's patients where the majority of patients are estrogen deficient and in girls with 'constitutional tall stature' where estrogen is used to decrease their final height by accelerating epiphyseal closure. In her consult, Dr. Beaston-Wimmer concluded that:

- In general, premature epiphyseal closure should not be a concern in females who are one-year post menarche.
- In the event Estrostep is given consideration as a primary therapy for the treatment of acne vulgaris, it would be prudent to consider recommending that all patients less than two years post menarche have a bone age assessment prior to treatment. To minimize the potential for reduction in final height, the bone age should be at least 15 years.

The question asked by HFD-540 in the current clinical consultation request is:

How was the issue of premature epiphyseal closure addressed in HFD-580?

MY CONCLUSIONS

The short answer to the above question is:

> In the past, the issue of premature epiphyseal closure was not felt by HFD-580 to be a concern and was not mentioned in any oral contraceptive labeling.

This is in agreement with the American College of Obstetrics and Gynecology Educational Bulletin #256, which states:

> Oral contraceptives do not cause premature closure of the epiphyses or inhibit skeletal growth. By the time menarche occurs, endogenous estrogen production has already initiated epiphyseal closure, and this process cannot be altered by exogenous steroids.[1]

I agree with Dr. Beaston-Wimmer that on review of the literature, no studies were found that specifically addressed the effects of oral contraceptives on the stature of adolescents. However, I was able to document that while the most frequently prescribed dose of ethinyl estradiol for adolescents with 'constitutional tall stature' to decrease final height was 0.1-0.5 mg per day, some Reproductive Endocrinologists have prescribed ethinyl estradiol 0.02 to 0.05 mg per day for the same indication.[2] I have not been able to document whether ethinyl estradiol 0.02 to 0.05 doses were felt to be effective for final height reduction, however these doses are similar to current oral contraceptives ethinyl estradiol doses.

The pivotal issue is whether estrogen decreases final height in postmenarcheal females. Several problems emerge if one evaluates the studies examining the use of estrogen for final height reduction as a surrogate for studies examining the effects of oral contraceptives on the stature of adolescents. One problem is that studies of estrogen for final height reduction frequently fail to report whether the treated subjects had reached menarche prior to the initiation of estrogens and/or whether untreated control subjects had reached menarche. Bartsch provided in a table the menarcheal status of treated patients from six of ten studies of estrogen for final height reduction.[3] In these six studies, a total of 234 estrogen treated adolescent girls had known menarcheal status and 85 were postmenarcheal. Sorgo provided in a table the menarcheal status of treated patients in 16 of 24 studies of estrogen for final height reduction.[4] In these sixteen studies, a total of 592 subjects treated with estrogen for final height reduction had known menarcheal status and 215 were postmenarcheal. The same reference listed only 2 studies where the menarcheal status of a total of 16 untreated controls was known and four were postmenarcheal. So the problem exists that the data from estrogen for final height reduction includes subjects that were premenarcheal and postmenarcheal at the initiation of estrogen treatment. The second problem is that estrogens for final height reduction studies frequently fail to report their results for the subgroups of those subjects who were premenarcheal at initiation of therapy and those subjects who were postmenarcheal at initiation of therapy. However, it is believed that most premenarcheal adolescents would experience menarche soon after estrogen treatment for final height reduction was initiated, so the majority of their treatment period would have been as a postmenarcheal adolescent.

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[1] ACOG; Ref #2
[2] Conte; Ref. #7
[3] Bartsch; Ref. #4
[4] Sorgo; Ref. #15

What has been reported is that the younger a girl was at the onset of estrogen treatment, the more her adult height could be reduced.[5] Porcu also reported that adolescent females during the first year after menarche had an incidence of 61.5% open epiphyses.[6]

I would add that the use of estrogen in Turner's patients may not be informative to this situation since the majority of Turner patients are estrogen deficient. However, studies in Turner patients are helping to elucidate the effect of estrogen in growth. Scientific data is available from studies in Turner patients that estrogens at low doses stimulate growth and estrogens at slighter higher doses inhibit growth.[7] Finally, the wide variation in the types of estrogen and the doses of estrogen administered to Turner patients and to reduce final height may limit their applicability to the current issue of whether postmenarcheal adolescents might develop premature epiphyseal closure from taking Estrostep® oral contraceptive pills.

In summary, I believe it is reasonable to conclude that estrogen treatment has resulted in reduced final height in 'constitutionally tall' postmenarcheal adolescent females. This conclusion raises the concern that oral contraceptives could potentially result in premature epiphyseal closure and a reduced final height in females who use oral contraceptives soon after menarche. However in my opinion, the reviewed scientific information is insufficient to reach a conclusion regarding whether oral contraceptive use in adolescent females is associated with premature epiphyseal closure and a reduced final height. I believe additional studies would be needed before the issue could be conclusively resolved. Until the situation is clearer, I recommend no change in the labeling language from what is in the currently approved class oral contraceptive labeling and in the currently approved Ortho Tri-Cyclen and Estrostep labels.

cc: NDA 21-276
NDA 20-130
HFD-580 Division File
HFD-580: S. Allen, D. Shames, D. Hixon, B. Gierhart, J. Mercier,
HFD-540: O. Cintron, J. Porres, J. Wilkin
HFD-510: P. Wimmer

References:

1) American College of Obstetrics and Gynecology. ACOG Technical Bulletin #145: The Adolescent Obstetric-Gynecologic Patient. September 1990 (Please note that this bulletin has been replaced with ACOG Educational Bulletin #254: Primary and Preventive Health Care for Female Adolescents. November 1999-both were reviewed).
2) American College of Obstetrics and Gynecology. ACOG Educational Bulletin #256: Oral Contraceptives for Adolescents: Benefits and Safety. December 1990. (Please note that this bulletin replaced the ACOG Committee Opinion #90: Safety of Oral Contraceptives for Teenagers February 1991-both were reviewed).
3) American College of Obstetrics and Gynecology. Adolescent Pregnancy Facts. No publication date provided (?1999).
4) Bartsch O et al. Oestrogen treatment of constitutionally tall girls with 0.1 mg/day ethinyl oestradiol. *Eur J Pediatr.* (1988) 147: 59-63.
5) Bierich J. Estrogen treatment of girls with constitutional tall stature. *Pediatrics.* (1978) 62; 6: 1196-1201.
6) Binder G. Outcome in tall stature. Final height and psychological aspects in 220 patients with and without treatment. *Eur J Pediatr.* (1997) 156: 905-910.
7) Bolton G. Adolescent Contraception. *Clinical Obstetrics & Gynecology.* (1981) 24 (3): 977-986.

[5] Bartsch; Ref. #4 and Sorgo; Ref. #15
[6] Porcu; Ref. #10
[7] Rotteveel; Ref. #12

8) Cacciari E et al. Final Height of Patients with Turner's Syndrome Treated with Growth Hormone (GH): Indications for GH Therapy Alone at High Doses and Late Estrogen Therapy. *The Journal of Clinical Endocrinology & Metabolism.* (1999) 84: 4510-4515.
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13) Hochberg Z and Zadik Z. Final Height in young women with Turner syndrome after GH therapy: an open controlled study. *European Journal of Endocrinology* (1999) 141: 218-224.
14) Levine L. Treatment of Turner's Syndrome with estrogen. *Pediatrics.* (1978) 62; 6: 1178-1183.
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16) Porcu E. Skeletal maturation and hormonal levels after the menarche. *Arch Gynecol Obstet.* (1994) 255 (1): 43-6.
17) Prader A and Zachmann M. Treatment of excessively tall girls and boys with sex hormones. *Pediatrics.* (1978) 62; 6: 1202-1210.
18) Rosenfield R et al. Optimizing Estrogen Replacement Treatment in Turner Syndrome. *Pediatrics* (1998) 102: 486-488.
19) Rosenfield R. Toward Optimal Estrogen-Replacement Therapy. *NEJM.* (1983) 309: 1120-1121.
20) Ross J et al. A Preliminary Study of the Effect of Estrogen Dose on Growth in Turner's Syndrome. *NEJM.* (1983) 309: 1104-1111.
21) Rotteveel J et al. Androstenedione, Dehydroepiandrosterone sulfate, and estradiol levels throughout female puberty: relation to height velocity. *Hormone Research.* (1997) 48: 263-267.
22) Segal S. Contraceptives and the Young: Present Status and Future Prospects. *Pediatrics.* (1978) 62; 6: 1211-1215.
23) Shoen E et al. Estrogen treatment of tall girls. *Am J Dis Child.* (1973) 125: 71-74.
24) Sorgo W et al. Critical analysis of height reduction in oestrogen-treated tall girls. *Eur J Pediatr.* (1984) 142: 260-265.
25) Weimann E and Brack C. Severe thrombosis during treatment with ethinylestradiol for tall stature. *Hormone Research.* (1996) 45: 261-263.
26) Wettenhall H et al. Tall girls: a survey of 15 years of management and treatment. *Adolescent Medicine.* (1975) 86; 4: 602-10.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

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FACSIMILE TRANSMISSION

DATE: December 4, 2000. Number of Pages (including cover sheet) - 1
TO: Joanna Hinton, PhD, Senior Manager, Worldwide Regulatory Affairs
COMPANY: Parke Davis
FAX#: 734-622-3283
MESSAGE: NDA 21-276 Estrostep Tablets

A request for information from the medical officer follow:

Please provide in a tabular format, if possible, the following information:

a. For each planned termination visit (PT), please provide the reason each one of the subjects was terminated early by the sponsor.

b. Many subjects have the letters "ET" entered in the VISIT variable, some times without a date, others with a date that is the same as the last previous visit, other times with a date that is later than the last recorded visit. Please provide clarification of what **"ET"** means and **how it was used.**

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

cc: original NDA 21-276
HFD-540/Price
HFD-540/Cintron

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
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FACSIMILE TRANSMISSION

DATE: March 21, 2001. Number of Pages (including cover sheet) – 1
TO: Joanna Hinton, Senior Manager, Regulatory Affairs
COMPANY: Parke Davis
FAX#: 734-622-3283

MESSAGE: RE: NDA 21-276 Estrostep Tablets - Treatment of acne

A request for information from Biopharm follow:

Following your response on March 16th to our request for specific raw pharmacokinetic data from studies 397 and 403 used to generate Figures 2 and 11 from report 764-03375, we recommend that you plot the following additional graphs and data analysis:

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

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FACSIMILE TRANSMISSION

DATE: May 1, 2001. Number of Pages (including cover sheet) – 2
TO: Ms. Joanna Hinton, Senior Manager, Regulatory Affairs
COMPANY: Parke Davis
FAX#: 734-622-3283

MESSAGE: RE: NDA 21-276, Estrostep Tablets for the treatment of acne vulgaris

In addition to the comments presented to the Applicant during the May 1, 2001, teleconference, regarding the 4/27/01 proposed draft labeling, the following text needs to be incorporated into the Brief Patient Labeling and Detailed Patient Labeling Sections:

Brief Patient Labeling

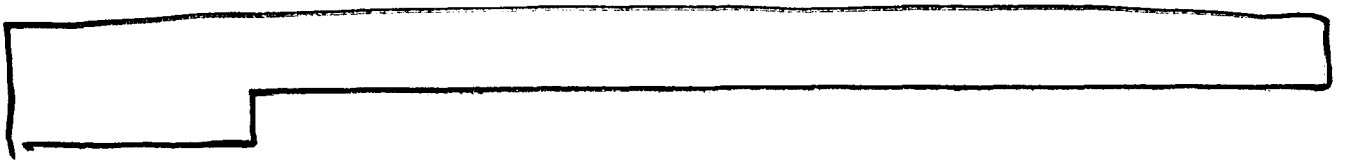
Various studies give conflicting reports on the relationship between breast cancer and oral contraceptive use. Oral contraceptive use may slightly increase your chance of having breast cancer diagnosed, particularly after using hormonal contraceptives at a younger age. After you stop using hormonal contraceptives, the chances of getting breast cancer begin to go back down. You should have regular breast examinations by a health care provider and examine your own breasts monthly. Tell your healthcare provider if you have a family history of breast cancer or if you have had breast nodules or an abnormal mammogram. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is a hormone-sensitive tumor.

[redacted]

Detailed Patient Labeling

Various studies give conflicting reports on the relationship between breast cancer and oral contraceptive use. Oral contraceptive use may slightly increase your chance of having breast cancer diagnosed, particularly after using hormonal contraceptives at a younger age. After you stop using hormonal contraceptives, the chances of getting breast cancer begin to go back down. You should have regular breast examinations by a health care provider and examine your own breasts monthly. Tell your healthcare provider if you have a family history of breast cancer or if you have had breast nodules or an abnormal mammogram. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is a hormone-sensitive tumor. Some studies have

found an increase in the incidence of cancer of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives.



FROM: Olga Cintron, R.Ph.
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