

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
20-874

ADMINISTRATIVE DOCUMENTS

ITEM 14. PATENT CERTIFICATION

CYCLO-PROVERA Contraceptive Injection

Request for Exclusivity

This application contains reports of new clinical investigations conducted or sponsored by the applicant (as defined under 21 CFR 314.108(a)) that are essential to approval of the application. Pharmacia & Upjohn therefore requests three (3) years of exclusivity for CYCLO-PROVERA Contraceptive Injection, pursuant to 21 CFR 314.108(4)(iv).

The following information is provided to assist in the determination of eligibility.

The Upjohn Company studied several formulations in a broad program to develop an injectable contraceptive product containing medroxyprogesterone acetate (MPA) and estradiol cypionate (E2C). The dose-ranging studies involving injectable MPA and E2C were sponsored by The Upjohn Company, and were conducted under IND — These studies were pivotal in the determination of the appropriate dose of the active ingredients in CYCLO-PROVERA

In addition, the three large adequate and well-controlled studies contained within this application which demonstrate the safety and efficacy of the product were sponsored and conducted by the World Health Organization (WHO). WHO licensed the worldwide rights to this clinical data to PATH/Concept Foundation. In 1994, PATH/Concept Foundation subsequently licensed to The Upjohn Company (now Pharmacia & Upjohn) the exclusive rights to this data for the United States and certain other countries.

No previous NDAs have been approved for this product for the "prevention of pregnancy" indication. Although some of the pivotal studies conducted by WHO have been reported in the public literature, Pharmacia & Upjohn has exclusive rights to the original study records (case record forms, SAS data sets, etc.) from these studies.

APPEARS THIS WAY
ON ORIGINAL

ITEM 13. PATENT INFORMATION

CYCLO-PROVERA Contraceptive Injection

- | | | |
|----|--|--|
| 1. | Active Ingredients | Medroxyprogesterone Acetate (MPA)
Estradiol Cypionate (E2C) |
| 2. | Strength | 25 mg MPA and 5 mg E2C |
| 3. | Tradename | CYCLO-PROVERA Contraceptive Injection |
| 4. | Dose Form and
Route of Administration | injectable suspension for intramuscular injection |
| 5. | Applicant Firm Name | Pharmacia & Upjohn Company |
| 6. | NDA Number | 20-874 |
| 7. | Approval Date | To be determined (no previous applications) |
| 8. | Exclusivity - date first
ANDA could be approved | Three (3) years after date of approval |
| 9. | Applicable unexpired
patent numbers | None |

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 20-874 SUPPL # N/A

Trade Name: Lunelle™ Monthly Contraceptive Injection
Generic Name: medroxyprogesterone acetate and estradiol cypionate

Applicant Name: Pharmacia & Upjohn HFD-580

Approval Date 10-5-00

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 questions about the submission.

a) Is it an original NDA? YES / / NO / /

b) Is it an effectiveness supplement? YES / / 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 / / 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.

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:

d) Did the applicant request exclusivity?

YES / / 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?

YES / / NO / /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 / /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 /___/

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 / /

APPEARS THIS WAY
ON ORIGINAL

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

NDA # 20-246 Depo-Prevera

NDA # 85-470 Estradiol Cypionate

NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. 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 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (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 9:**

-
- (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 /

- (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: _____

APPEARS THIS WAY
ON ORIGINAL

(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 /_X_/

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, Study # M5415/0004

Investigation #2, Study # m/5415/0006

Investigation #3, Study # _____

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_/

Investigation #3 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:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(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_/

Investigation #3 YES /___/ NO /__X_/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(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 #__, Study # M/5415/0004

Investigation #__, Study # M/5415/0006

Investigation #__, Study # _____

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.

APPEARS THIS WAY
ON ORIGINAL

(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 # 52,624 YES / X / ! NO / ___ / Explain: _____

Investigation #2
IND # 52,624 YES / X / ! NO / ___ / Explain: _____

Investigation # 3
IND # 52,624 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?

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: _____

LS
(Signature of Preparer
Title: _____

9/27/00
Date

LS
Signature of Office of Division Director

9/27/00
Date

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac

EXCLUSIVITY SUMMARY FOR NDA # 20-874

SUPPL # _____

Trade Name Lunelle™ Monthly Contraceptive Injection

Generic Name medroxyprogesterone acetate and estradiol cypionate

Applicant Name Pharmacia & Upjohn Company

HFD # 580

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 / /

b) Is it an effectiveness supplement?
YES / / 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 / / 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.

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:

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# 20-246 _____ Depo-Provera _____

NDA# 85-470 _____ Estradiol Cypionate _____

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 / / 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 / / 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 / /

APPEARS THIS WAY
ON ORIGINAL

(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 / /

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 / /

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:

M/5415/0004

M/5415/0006

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.

APPEARS THIS WAY
ON ORIGINAL

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 / /

Investigation #2 YES / / NO / /

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 / /

Investigation #2 YES / / NO / /

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"):

M/5415/0004

M/5415/0006

APPEARS THIS WAY
ON ORIGINAL

(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 / /

If yes, explain: _____

/S/

Signature

Title: _____

10/5/99
Date

/S/

Signature of Office/
Division Director

10/6/99
Date

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

APPEARS THIS WAY
ON ORIGINAL

ITEM 16. DEBARMENT CERTIFICATION

Cyclo-Provera Contraceptive Injection

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that, to the best of its knowledge and belief, the applicant did not and will not use in any capacity the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act in connection with this application.

|S|

9/04/97

Ed L. Patt
Manager
Regulatory Compliance

Date

APPEARS THIS WAY
ON ORIGINAL

DEBARMENT CERTIFICATION FOR AMENDMENT TO NDA 20-874

**CYCLO-PROVERA Contraceptive Injection
(Amendment to NDA 20-874)**

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that, the applicant did not and will not use in any capacity the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act in connection with this application.

/S/

4/12/99

Ed L. Patt
Manager
Regulatory Compliance

Date

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 20-874

Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFU-570 Trade and generic names/dosage form: acetone & corallin ^(medicinal preparation) Action: AP AE (NA)

Applicant Pharmacia & Upjohn Therapeutic Class _____

Indication(s) previously approved NA

Pediatric information in labeling of approved indication(s) is adequate inadequate _____

Proposed indication in this application Prevention of Pregnancy

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? Yes (Continue with questions) No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

Neonates (Birth-1month) Infants (1month-2yrs) Children (2-12yrs) Adolescents(12-16yrs)

1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.

a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

c. The applicant has committed to doing such studies as will be required.

(1) Studies are ongoing.

(2) Protocols were submitted and approved.

(3) Protocols were submitted and are under review.

(4) If no protocol has been submitted, attach memo describing status of discussions.

d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? Yes No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Medical Review (e.g., medical review, medical officer, team leader)

Signature of Preparer and Title CSO

Date 4/5/88

Orig NDA/BLA # _____

HF _____ /Div File

NDA/BLA Action Package

HFD-006/ KRoberts

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

(revised 10/20/97)

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

ADA Number: 020874 **Trade Name:** CYCLO-PROVERA CONTRACEPTIVE INJ(ESTRADIO +
Supplement Number: 000 **Generic Name:** ESTRADIOL CYPIONATE/MEDROXYPROGESTERONE
Supplement Type: N **Dosage Form:**
Regulatory Action: **COMIS Indication:** PREVENTION OF PREGNANCY
Action Date: **AP**

10-5-00

Indication # 1 Contraception

Label

Adequacy: 4

Formulation

Needed: 0

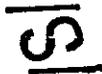
Comments (if any): Safety and efficacy of Lunelle Monthly Contraceptive Injection have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under 16 years of age and users 16 years of age and older. Use of this product before menarche is not indicated.

Lower Range	Upper Range	Status	Date
Tanner5	Adult	Waived	10/4/00

Comments: Safety and efficacy of Lunelle Monthly Contraceptive Injection have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under 16 years of age and users 16 years of age or older. Use of this product before menarche is not indicated.

This page was last edited on 10/4/00

(Signature -



Date

10/4/00

APPEARS THIS WAY
ON ORIGINAL

Office of:
P.K. Narang, Ph.D., F.C.P.
Liaison Director, New Drugs
Global Regulatory Affairs

Telephone No. (616) 833-9896
Facsimile No. (616) 833-8237

October 5, 2000

Susan Allen, M.D.
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

**RE: NDA 20-874
Lunelle Monthly Contraceptive Injection
(Medroxyprogesterone acetate and Estradiol
cypionate Injectable Suspension)**

LABELING: Insert

Dear Dr. Allen

Pursuant to a call from Ms. Mercier this morning, the requested change under WARNINGS (Item 6; paragraph 5, last line) has been made per Division's guidance.

Attached please find a revised (FINAL) clean copy of Physician (pi) insert for Lunelle Monthly Contraceptive Injection.

- | | |
|---------------------|-----------------------------------|
| 1. Physician Insert | (Version 10.5.2000; Attachment 1) |
| - pi1005.doc | (clean WORD 6.0 copy) |
| - pi1005.pdf | (pdf file format) |

A copy of these files was sent electronically via e:mail to Ms. Mercier earlier today and

are also placed on the enclosed CD-ROM. The enclosed transport media was checked using VirusScan NT (version 7) and deemed 'virus free'. Though P&U has taken needed precautions, use of a similar software by CDER is encouraged for added assurance.

Should there be any questions regarding this submission, please contact me at (616) 833-9896. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

P.K. Narang, Ph.D., F.C.P.
Director
Global Regulatory Affairs

PKN:

Attachments

cc: Jennifer Mercier (Desk Copy)

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

.e: 10/5/00 10:49:56 AM
From: _____
To: mercierj
Cc: _____ (mercierj@A1)
Subject: LUNELLE Physician PI - 10/5 version

Hi Jen

Here is the new version (pi1005.doc), per Division's guidance. Let me know when you are the FAX machine .. to FAX.

My cover letter (let22.doc) for the submission being overnighted today is also attached.

take care...!! Call me and let me know.

thanks

P.K.

APPEARS THIS WAY
ON ORIGINAL

Division Director Memorandum

OCT 5 2000

NDA#: 20-874

Drug: Lunelle™ Monthly Contraceptive Injection

Generic Drug Name: Medroxyprogesterone acetate and estradiol cypionate injectable suspension

Indication: Prevention of pregnancy

Dose: 25 mg medroxyprogesterone acetate and 5 mg estradiol cypionate intramuscular injection for monthly administration

Administration: Intramuscular injection every 28 to 30 (not to exceed 33) days

Formulation: Injectable suspension

Applicant: Pharmacia & Upjohn Company

Date of submission: April 7, 2000

Date of memorandum: October 5, 2000

Background

Lunelle™ Monthly Contraceptive Injection (Lunelle™) is an injectable drug product containing 25 mg of medroxyprogesterone acetate (MPA) combined with 5 mg of estradiol cypionate. The product is to be administered intramuscularly every 28 to 30 (not to exceed 33) days for female contraception. Currently, Depo-Provera® [medroxyprogesterone acetate injectable suspension] (DMPA) is the only injectable contraceptive product approved for use in the United States. It is a progestin-only contraceptive method that is administered by intramuscular injection every three months.

The most common reason for discontinuation of either oral or injectable progestin-only contraceptive methods is disruption of menstrual bleeding patterns, resulting in unsatisfactory acceptability profiles for these products. Lunelle™ was developed as an alternative to DMPA, having an estrogen component added in an attempt to increase the incidence of regular menstrual bleeding patterns and enhance the product's acceptability.

Lunelle™ is marketed as a contraceptive in several countries outside the United States where it is known as CYCLO-PROVERA™. An NDA for this product was submitted to the Division of Reproductive and Urologic Drug Products (DRUD) of the FDA on September 25, 1997. The application contained the results from three phase 3 clinical trials sponsored by the World Health Organization (WHO) and thirty-eight additional clinical trials that provided supportive safety and/or efficacy data for the product. Numerous deficiencies were found in the database contained in the original application, resulting in issuance of a not-approvable letter to the sponsor on September 25, 1998. The sponsor subsequently submitted an amendment to the NDA on April 16, 1999 in response to the deficiencies noted in the not-approvable letter.

Prior to submission of the original NDA in 1997, the sponsor had initiated a large U.S. trial (study M/5415/0004) to evaluate the acceptability, efficacy and safety of the product when used by U.S. women. This trial was designed primarily as an acceptability trial, but data on efficacy and safety were also collected. The trial was a non-randomized, open-label, comparative trial of CYCLO-PROVERA™ and Ortho-Novum 7/7/7-28 tablets in 1,100 volunteers. Results from this trial comprised the amendment submitted on April 16, 1999 and were found to be supportive of marketing approval for the product in the U.S. However, On October 1, 1999, during an FDA inspection of the sponsor's Kalamazoo, MI manufacturing site, significant Good Manufacturing Practices (GMP) deficiencies at the site were discovered, resulting in a recommendation to withhold approval of the product by the Office of Compliance. Subsequently, an approvable letter for the application was sent to the sponsor on October 15, 1999.

Review of the Current Submission

The current submission contains results from an ongoing extension to trial M/5415/0004. This extension trial (study _____) is being conducted to obtain additional safety and efficacy information on continued, long-term use of Lunelle Monthly Contraceptive Injection. The submission also contains results from a repeat site inspection of the Kalamazoo, MI manufacturing facility, revised physician and patient labeling and a draft summary of a proposed phase 4 commitment study assessing the effects of Lunelle™ on bone mineral density (BMD).

A repeat site inspection of the manufacturing facility was conducted from March 20-31, 2000 and resulted in an "acceptable" recommendation from the Office of Compliance. Key clinical review issues noted during the prior review cycle for this application included (1) the effect of the product on menstrual bleeding patterns in users and (2) the adequacy of justification for the estradiol cypionate component of the product.

Effect of Lunelle™ on menstrual bleeding patterns:

As described in my previous secondary review dated September 20, 1999, there was insufficient evidence that Lunelle™ produced a more regular bleeding pattern than DMPA if bleeding patterns other than amenorrhea were studied. Also as described in that review, the data from

study M/5415/0004 did not support the sponsor's assertion that Lunelle Monthly Contraceptive Injection increased the incidence of regular menstrual bleeding patterns in users. It was noted that 58.6% of patients using Lunelle™ in that study had clinically undesirable bleeding patterns during the fourth reference period (corresponding to months 9 to 12 of use), while 41.4% had "normal" bleeding patterns during this use period. Bleeding patterns did not predict discontinuation from the trial nor did they pose a safety risk in that the incidence of anemia throughout trial M/5415/0004 was reported as 1.3% and that for trials M/5415/0004 and combined was 1.7%.

In the current submission, the sponsor again examined the effects of Lunelle™ use on menstrual bleeding patterns in women participating in study ————. As noted in the primary Medical Officer's review, use of Lunelle™ was associated with less desirable bleeding patterns than use of continuous oral contraception (Ortho-Novum 7/7/7), with a higher percentage of Lunelle™ users having either longer withdrawal bleeding episodes (bleeding lasting more than 7 or 10 days) or amenorrhea than women using Ortho-Novum 7/7/7. The percentage of women having a withdrawal bleed of 3-7 days was much lower in Lunelle™ users (48%) than in Ortho-Novum 7/7/7 users (85%) throughout the study. This does not support the sponsor's assertion that bleeding patterns associated with use of Lunelle™ are similar to those noted with oral contraceptives.

Justification of the estrogen-component of Lunelle™.

According to the sponsor, the rationale for the addition of estradiol cypionate to the progestin component of this product was to improve bleeding patterns over those typically seen with progestin-only contraceptives, particularly DMPA. As described above, this benefit was not demonstrated from the data provided by the sponsor in the past or current submissions. In addition, although the sponsor claimed that the estrogen component of the product was associated with a reduced risk of breakthrough ovulation, data contained in the submitted applications did not support this position. However, the addition of the estrogen component was justified for other reasons as described below.

The sponsor provided historical data comparing ovulation rates in users of progestin-only oral contraceptives and progestin containing contraceptive implants. The sponsor also provided data from a small study (M/5415/0012) describing sonographic assessment of ovarian follicular activity in two groups of 15 women receiving 2 cycles of either Lunelle™ or Alesse-28 (a combined oral contraceptive containing 20 µg of ethinyl estradiol and 0.1 mg of levonorgestrel). The results of this study showed a statistically significantly lower rate of follicular development in Lunelle™ users versus combined oral contraceptive users. However, it did not compare follicular activity of Lunelle™ with the same dose of MPA alone, nor with DMPA, thereby making it difficult to ascertain the effect of the estrogen component of Lunelle™ on ovulation rate.

Results of a pharmacokinetic and pharmacodynamic study contained in the NDA demonstrated that, following treatment discontinuation, ovulation returned earlier in women receiving Lunelle™ or a half-strength formulation of the product as compared to those who received the same respective doses of MPA alone. This finding does provide justification for the estrogen component of the product.

Safety data contained in the original application, the 1999 amendment to that application and the current submission did not demonstrate an increased risk for estrogen-related serious adverse events and supported the safety of Lunelle™ as a monthly contraceptive. The most common adverse event leading to discontinuation of Lunelle™ treatment was weight gain. Wide variability in individual weight gain or loss was observed in trials M/5415/0004 and _____, however, an increasing percentage of Lunelle™ users in these clinical studies exhibited weight change in excess of 10 and 20 pounds with continued treatment. This information was incorporated into product labeling.

Despite the lack of evidence for improvement in bleeding patterns as compared to DMPA, Lunelle™ appears to offer the following advantages over injectable progestin-only contraceptives: (1) a reduced incidence of amenorrhea with continued use; (2) more rapid reversibility of drug effect following discontinuation; (3) more rapid return to fertility following product discontinuation.

The labeling for Lunelle™ was extensively revised from the original version submitted by the sponsor. The final format and content of the information contained in the label was designed to reflect data known and risks associated with combined hormonal contraceptives and with progestin-only injectable contraceptive products. Product specific information related to the effects of Lunelle™ on weight change and bleeding patterns were also incorporated into the label. All relevant comments specific to this product from each review discipline were included in the final label dated October 5, 2000.

During the previous review cycle, at the request of the Director of the Office of Drug Evaluation III, a "Clinical Studies" section was added to the proposed Lunelle™ label. This section contains a description of study M/5415/0004 including the patient population studied, summary efficacy results and summaries of key safety issues, namely bleeding pattern alterations and weight change during product use.

At the time of issuance of the approvable letter dated October 15, 1999, the sponsor agreed to conduct one or more phase 4 studies to assess potential benefits of Lunelle™ over an MPA-alone product. These studies were to examine the effects of Lunelle™ on bleeding patterns, return to ovulation and BMD. With the results from the previously noted pharmacodynamic study demonstrating a faster return to ovulation with Lunelle™ as compared to MPA-alone products, a single phase 4 study was recommended by DRUDP and agreed to by the sponsor during the current review cycle. This study will evaluate the theoretical effects of Lunelle™ on BMD and

will compare these results to those of DMPA over a 2-year treatment period. Specific modifications in the design of this phase 4 study were requested of and agreed to by the sponsor during a teleconference on October 3, 2000. The sponsor agreed to submit a final protocol for this phase 4 study within 6 months of product approval.

Conclusions and Recommendations

Data contained in the 1999 amendment to the original NDA and in the current submission does support the safety and effectiveness of Lunelle™ for marketing approval in the U.S. As noted above, the sponsor will conduct a phase 4 commitment study to further assess the theoretical benefits of the estrogen component of Lunelle on BMD.

I agree with the primary reviewers' assessments and recommend approval of Lunelle™ for the indication of female contraception.

S

WMD 10/5/00

Susan S. Allen, MD, MPH
Director, Division of Reproductive and Urologic Drug Products

Cc: NDA 20-874
HFD-580, Division File
HFD-103
SAllen, DHixon

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 10/4/00 4:08:32 PM
From: _____
To: mercierj (mercierj@A1)
Subject: NDA 20-874 Cyclo-Provera

Hi Jen

Here is the modified cover letter as you requested this afternoon. Let me know if this addresses your needs. We are getting down to the last day. Appreciate you letting me know that action could happen tomorrow. Just advise me before you are ready to FAX. This letter has been sent by overnight mail as well and you should get the submission sent earlier this afternoon and the letter at the same time (its addressed to Dr. Allen). I have stated that this letter supersedes the previous one. Hope that is OK? let me know.

rgds

P.K.

Forward Header

Subject: NDA 20-874 Cyclo-Provera
Author: _____
Date: 10/4/00 3:47 PM

The attached letter supersedes the letter included in the labeling submission sent earlier this morning and may be appended to it. Information requested by the Division is now shown in BOLD text.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

MEMORANDUM

OCT 4 2000

To: NDA 20-874

From: Dena R. Hixon, MD, FACOG
Medical Officer, DRUDP

Date: October 4, 2000

Re: **Review of July 11, 2000 submission :**

- Phase IV Bone Mineral Density study proposal
- Proposed labeling changes based on Reanalysis of Bleeding Patterns

As noted by Dr. Scott Monroe in his review of this submission, the sponsor proposes a 2-year randomized comparative study of Lunelle™ Monthly Contraceptive Injection vs. DMPA in 1380 women 18-35 years of age (920 receiving Lunelle™ Monthly Contraceptive Injection and 460 using DMPA) evaluated by DXA at screening and at 6-months intervals for lumbar spine, hip, and total body BMD. The proposed primary endpoint is the percent of subjects in each treatment group experiencing BMD loss. An imputation for any missing DXA value after baseline in the intent to treat analysis is proposed.

The sponsor's power calculations indicate that a sample size of 276 patients in the Lunelle group and 138 in the DMPA group will give 80% power with an overall type I error ≤ 0.05 to detect a difference of 15% in the response rate in BMD loss between the two treatment groups. Assuming a drop out rate of 70% after 2 years, then 920 patients would be needed in the Lunelle treatment group and 460 in the DMPA group.

Reviewer's comments

- The sponsor should modify the primary endpoint to the percent change from baseline in bone mineral density at 1 and 2 years after initiating treatment as measured by DXA.
- Imputation of missing data is not appropriate.

The sponsor has presented the following proposals for labeling based on the reanalysis of bleeding patterns.

1. In the PI, CLINICAL STUDIES section, as the third paragraph:

[Redacted content]

Reviewer's comments

- A. The above paragraph is not an accurate representation of the findings in the reanalysis. It implies that bleeding patterns seen with Lunelle™ are similar to those seen with oral contraceptives. It also implies that individual women were followed over time and found to have

similar bleeding patterns from cycle to cycle. In fact, the re-analysis evaluated the number and percent of women in each individual cycle that reported bleeding on various cycle days and duration of bleeding episodes. It is unknown whether the patterns seen in a given cycle are indicative of an individual's bleeding pattern over an entire year of treatment with Lunelle™ Monthly Contraceptive Injection.

- B. Comparing bleeding patterns between two hormonal contraceptive methods with very different withdrawal bleeding intervals (7 days for OCs vs. 14 or more days for Lunelle™) is not appropriate.
- C. Whereas this is a post hoc reanalysis of bleeding patterns and not the endpoint designed for the phase 3 trials, it is not ideal to include this information in the labeling at all. However, information based on monthly cycles instead of 90-day intervals, as in the original study report, may be more clinically meaningful to clinicians.
- D. The following modification is recommended:

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E. A CLINICAL STUDIES section has not been included in previous labels for hormonal contraceptives. If included in a CLINICAL STUDIES section, this paragraph should be moved to the 5th paragraph.

- 2. In the PPI, SIDE EFFECTS OF LUNELLE™ MONTHLY CONTRACEPTIVE INJECTION, Subsection 1, Vaginal bleeding, change as follows:

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Reviewer's comment

The above paragraph does not accurately present the bleeding abnormalities reported in the NDA.

The following modification is recommended:

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T _____]

Recommendations

- The above comments regarding the proposed Phase IV study were communicated to the sponsor on October 3, 2000, and the sponsor committed to the requested change in primary endpoint and not to impute missing data points. The sponsor will submit a final protocol within 6 months of approval.
- Labeling recommendations from all disciplines have been reviewed and incorporated into labeling as appropriate. On October 3, 2000, final labeling revisions were negotiated with the sponsor.

IS

10/4/00

Dena R. Hixon, M.D., FACOG
Medical Officer, DRUDP

S

10/4/00

Susan S. Allen, M.D., M.P.H.
Director, DRUDP

Cc: NDA 20,874 Division File/ HFD-580/S. Allen/ D. Hixon/J Mercier

APPEARS THIS WAY
ON ORIGINAL

Pharmacia & Upjohn

Global Regulatory Affairs

Director, Regulatory Liaison, New Drugs

For operator assistance call 616-833-6966

To: Ms. Jennifer Mercier, DRUDP	
Fax No: 301-827-4267	
Subject: Lunelle Labeling (NDA 20-874): Pharmacia Version, October 3, 2000	
Copies:	
From: _____	
Tel No: _____	Fax No: _____
Date: 10-3-00	Pages (including this one): 5

Dear Jen:

PHA appreciates the efforts of the Division in enhancing the labeling for Lunelle MCI. Most of the labeling changes suggested by the Division have been accepted, except those provided in the attached pages as our proposal for further enhancing balance and clarity. The noted line numbers refer to the FDA version of October 2, 2000.

PI:

Section-Clinical Studies:

The first page refers to lines 206-216.

Section-Precautions: Weight Change

The next page refers to lines 688-703

PHARMACIA & UPJOHN, 7000 Portage Road, Kalamazoo, MI 49001

Confidentiality Note: The documents accompanying this telecopy transmission contain information belonging to Pharmacia & Upjohn, which is intended only for the use of the addressee. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution or the taking of any action in reliance on the contents of this telecopied information is strictly prohibited. If you have received this telecopy in error, please immediately notify us by telephone to arrange for the return of the original documents to us. Thank you.

PPI:

Section Side Effects... : Vaginal Bleeding

The next page refers to Lines 276 -279

Since the time is short, rather than sending the complete labeling to you, we thought it would be better if we reached consensus with you during the telecon (today at 3:15 pm) and then send the final version to you positively by tomorrow. All changes are highlighted.

The telephone no. for t-con 877 327 5618 (code: 556104)

Call me if there are any questions. At 616 833 9896 or my mobile 616 330 7541.

Regards!

P.K. Narang

APPEARS THIS WAY
ON ORIGINAL

PHARMACIA & UPJOHN, 7000 Portage Road, Kalamazoo, MI 49001

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Teleconference Minutes

Date: October 3, 2000

Time: 3:15 – 4:00 PM

Location: Parklawn; 17B-43

NDA 20-874

Drug: Lunelle™ Monthly Contraceptive Injection
(medroxyprogesterone acetate/ethinyl estradiol)

Indication: contraceptive

Sponsor: Pharmacia & Upjohn

Type of Meeting: Labeling

FDA Attendees:

Dena Hixon, M.D. – Medical Officer, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Scott Monroe, M.D. – Medical Officer, DRUDP (HFD-580)

Jennifer Mercier, B.S. – Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:

Roger Garceau, M.D. - Clinical Development, Pharmacia & Upjohn

Charles Wajszczuk, M.D. - Clinical Development, Pharmacia & Upjohn

Henk deKoning Gans, M.D. - Clinical Development, Pharmacia & Upjohn

P.K. Narang, Ph.D. - Global Regulatory Affairs, Pharmacia & Upjohn

Carl DeJuliis, M.S. - Global Reg. Affairs, Pharmacia & Upjohn

Cynthia Greenwald, M.S. - Biostatistics, Pharmacia & Upjohn

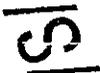
Chris Bilkey - Global Business Management, Pharmacia & Upjohn

Colette Andrea - Global Business Management, Pharmacia & Upjohn

Meeting Objective: To negotiate final labeling for this drug product.

Decisions made:

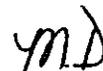
- the Division will require one phase 4 commitment to study bone mineral density study
- the sponsor agrees to submit the protocol within six months post-approval and receive Division agreement prior to study initiation
- the sponsor agrees that the primary endpoint of this study will be modified to '% change from baseline' and the test between the arms will consider the sensitivity related to measurement error
- the sponsor also agrees that the protocol will not propose to impute any missing DXA data
- Labeling: See attached label.



Minutes Preparer



Concurrence, Chair



cc:

Original NDA

HFD-580/DivFile

HFD-580/Rumble/Mercier

HFD-580/Allen/Shames/Hixon/Monroe

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

35 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

MEMORANDUM

To: NDA 20-874

Through: Gerald Willett, MD
Acting Team Leader, HFD-580

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

Date: August 7, 2000

Re: Lunelle Monthly Contraceptive Injection
(Medroxyprogesterone Acetate and Estradiol Cypionate Injection)
N-BM (Minor Clinical Amendment)
1. Phase IV Commitment: Bone Mineral Density Study
2. Additions to Physician Insert (PI) and Patient Package Insert (PPI)

Date of Submission: July 11, 2000
Date Submission Received: July 12, 2000

15
10/4/00
10/2/00
CD

Current submission:

This submission contains:

- Modified Bone Mineral Density Study proposal- to be reviewed by Dr. Scott Monroe
- Additions to PI and PPI regarding using monthly bleeding analysis for Lunelle™ Monthly Contraceptive Injection. The Sponsor has reanalyzing the bleeding data from the US clinical trial M/5415/004 using the one-cycle analysis of bleeding patterns (see Attachment 4). The data was originally analyzed by the WHO 90-day menstrual bleeding patterns as described by Belsey. The Sponsor contends that providing the one-cycle bleeding pattern information in the CLINICAL STUDIES Section (June 28, 2000 Version lines 184-193) would benefit patient-physician communications allowing for an educated decision making.
- Expected bleeding irregularities according to the WHO 90-day menstrual bleeding patterns analysis are already discussed in the Lunelle PI CLINICAL STUDIES Section (June 28, 2000 Version lines 196-206), in the Lunelle PI WARNINGS Section, Subsection 11. BLEEDING IRREGULARITIES (June 28, 2000 Version lines 616-634), and in the Lunelle PPI 1. Vaginal Bleeding Subsection (June 28, 2000 Version Lines 271-287).

Review of Other Contraceptive Labels:

- There was no precedent found for placing bleeding information in contraceptive labels anywhere except under the WARNINGS Section. A prescriber would not anticipate seeing any bleeding information to be in the CLINICAL STUDIES Section. A prescriber would not anticipate seeing a CLINICAL STUDIES Section in a contraceptive label.
- Depo-Provera PI has no CLINICAL STUDIES Section and only provides clinical trial data regarding pregnancy rates in the INDICATIONS AND USAGE Section. Depo-Provera PI only discusses bleeding irregularities in the WARNINGS Section, Subsection 1. *Bleeding Irregularities*. Depo-Provera PI WARNINGS Section, Subsection 1. *Bleeding Irregularities* uses language similar to the WARNINGS Section, Subsection 11. BLEEDING IRREGULARITIES of the Lunelle label, except Depo-Provera PI provides the additional information regarding amenorrhea rates:

By month 12 amenorrhea was reported by 55% of women, and by month 24 amenorrhea was reported by 68% of women using DEPO-PROVERA Contraceptive Injection.

- Norplant PI has no **CLINICAL STUDIES** Section and only provides clinical trial data regarding pregnancy rates in the **INDICATIONS AND USAGE** Section. Norplant PI only discusses bleeding irregularities in the **WARNINGS** Section, Subsection 2. *Bleeding Irregularities*. Norplant PI **WARNINGS** Section, Subsection 1. *Bleeding Irregularities* uses language similar to the **WARNINGS** Section, Subsection 11. **BLEEDING IRREGULARITIES** of the Lunelle label, except Norplant PI provides the additional information regarding cancer, pregnancy, and anemia:

Irregular bleeding patterns associated with the NORPLANT SYSTEM could mask symptoms of cervical or endometrial cancer. Overall, these irregularities diminish with continued use. Since some NORPLANT SYSTEM users experience periods of amenorrhea, missed menstrual periods cannot serve as the only means of identifying early pregnancy. Pregnancy tests should be performed whenever a pregnancy is suspected. Six (6) weeks or more of amenorrhea after a pattern of regular menses may signal pregnancy. If pregnancy occurs, the capsules must be removed.

Although bleeding irregularities have occurred in clinical trials, proportionally more women had increases rather than decreases in hemoglobin concentrations, a difference that was highly significant. This finding generally indicates that reduced menstrual blood loss is associated with the use of the NORPLANT SYSTEM. In rare instances, patients experienced heavy bleeding that resulted in hemoglobin values consistent with anemia.

- Oral contraceptive PI for Brevicon, Demulen 1/35 & 1/50, Levlen, Levlite, Loestrin 1/20 & 1.5/30, Lo/Ovral, Mircette, Micronor, Modicon, Nordette-28, Norinyl 1+35 & 1+50, Ortho-Novum 7/7/7, 10/11, 1/35 & 1/50, Ovral, Ovrette, Ovcon 35 & 50, Tri-Levlen, Tri-Norinyl, and Tri-phasil have no **CLINICAL STUDIES** Section, do not discuss specific clinical trials, and bleeding irregularities are only discussed in the **WARNINGS** Section, Subsection 11. **BLEEDING IRREGULARITIES** following current Labeling Guidance for Oral Contraceptives, which markedly differs from the same subsection in the Lunelle PI. The Draft Guidance for Combined Oral Contraceptives (COCs)-Labeling for Health Care Providers and Instructions for Use (August 1999) changes subsection 11 Bleeding Irregularities.to:

6. Unexplained vaginal bleeding

Women who have unexplained vaginal bleeding, suggestive of an underlying pathological condition or pregnancy, should be evaluated prior to initiation of COC use to avoid confusion of the potentially pathologic bleeding with a possible COC side effect.

Mild bleeding irregularities are common among women taking COCs, particularly during the early months of use. However, if the bleeding pattern of a COC user is suggestive of pathology or pregnancy, diagnostic measures should be taken to rule out these other causes; meanwhile, the benefits of continued COC use generally outweigh the risks.

The above Draft Guidance Subsection 6. Unexplained vaginal bleeding also markedly differs from the similar subsection in the Lunelle PI.

- Alesse, Ortho-Cept, Ortho-Cyclen, and Desogen have no **CLINICAL STUDIES** Section and only provide clinical trial data regarding pregnancy rates in the **INDICATIONS AND USAGE** Section. Bleeding irregularities are only discussed in the **WARNINGS** Section, Subsection 11. **BLEEDING IRREGULARITIES** following current Labeling Guidance for Oral Contraceptives, which markedly differs from the same subsection in the Lunelle PI.
- Ortho Tri-Cyclen PI has no **CLINICAL STUDIES** Section and provides clinical trial data regarding pregnancy rates and acne in the **INDICATIONS AND USAGE** Section. Bleeding irregularities are only discussed in the **WARNINGS** Section, Subsection 11. **BLEEDING IRREGULARITIES** following current Labeling Guidance for Oral Contraceptives, which markedly differs from the same subsection in the Lunelle PI.

- NuvaRing November 30, 1999 PI Draft Labeling has a **CLINICAL STUDIES** Section which only discusses the bleeding patterns in the studies and does not provide clinical trial data in the **INDICATIONS AND USAGE** Section. Bleeding irregularities are also discussed in the **WARNINGS** Section, Subsection 11. **BLEEDING IRREGULARITIES** following current Labeling Guidance for Oral Contraceptives, which markedly differs from the same subsection in the Lunelle PI.

Recommendations:

1) **Reject Sponsor's June 28, 2000 version Proposed US Patient Package Insert changes highlighted in yellow to Lines 272-278. Maintain previous wording.**

2) [_____]

3) **Clinical data from Lunelle PI CLINICAL STUDIES Section regarding pregnancy rates should be moved to the INDICATIONS AND USAGE Section**

4) **Clinical data from Lunelle PI CLINICAL STUDIES Section regarding bleeding patterns should be moved to WARNINGS Section, Subsection 11. BLEEDING IRREGULARITIES in truncated form to match Depo-Provera PI. Lunelle should list amenorrhea rates in this subsection, as does the Depo-Provera PI.**

5) [_____]

•
•
•

[_____]

6) [_____]

[_____]

7) **If reanalysis of data is permitted in CLINICAL STUDIES section, recommending rejecting Sponsor's June 28, 2000 version Proposed US Patient Package Insert changes highlighted in yellow to Lines 184-193. Recommend Lines 170 to 195 of the June 28, 2000 be replaced with the following:**

CLINICAL STUDIES

Due to certain limitations of the available data (loss to follow-up, lack of pregnancy testing, use of barrier contraceptive products and concomitant medications, etc.), a precise estimate of the failure rate is not possible, but is likely in the range of 0.1-1%.
(**Will need to have Statistics review Sponsor's calculations and assist in calculating % with Withdrawal Bleeding lasting 10 or more days).

**APPEARS THIS WAY
ON ORIGINAL**



Food and Drug Administration
Rockville, Maryland 20857

MEMORANDUM

Date: September 27, 2000

From: Jerry Phillips, R.Ph., Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

Through: Jennifer Mercier
Project Manager, HFD-580

To: Susan Allen, MD, Director, Division of Reproductive and Urologic Drug Products

Subject: Trademark consultation for Lunelle Monthly Contraceptive Injection (NDA 20-874)

IS

9/27/00

The proposed proprietary name, Lunelle, was reviewed on 5/11/2000 (OPDRA consult 00-0132) and was found acceptable by the Office of Post-Marketing Drug Risk Assessment. OPDRA also finds the Monthly Contraceptive Injection acceptable as the trademark for Pharmacia and Upjohn's norgestrel and norgestrel/levonorgestrel progestin and estradiol cypionate injectable suspension.

APPEARS THIS WAY
ON ORIGINAL



Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000



September 12, 2000

Dr. Susan Allen, Director
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-874
Lunelle™ Monthly Contraceptive Injection
(Medroxyprogesterone acetate and Estradiol
cypionate Injectable Suspension)

General Correspondence
Chemistry: Correction of the Impurity Limits

Dear Dr Allen:

We would like to bring to your attention, a recently discovered inadvertent error in the Lunelle Monthly Contraceptive Injection (previously referred to as Cyclo-Provera) new drug application (NDA 20-874). Therefore, in accordance with 21 CFR § 314.60 (a), we are amending New Drug Application NDA 20-874 with this minor information correction item.

Specifically, the impurities limits for two of the impurities (MPA and MPA) of the drug substance medroxyprogesterone acetate were reversed. Please refer to Item 4A, Chemistry, Manufacturing and Controls, Part ID, Drug Substance, page 4/1/43 of the current NDA that was submitted in September 1997. The correct limits are:

MPA impurity: NMT
MPA impurity: NMT

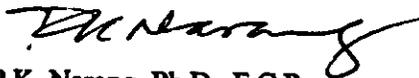
For convenience, a corrected copy of this page is provided in Attachment 1. Note that the above correction is in agreement with our amendment to Drug Master File dated August 29, 1997 (see Attachment 2). Batch data to support the corrected impurity limits is shown in Table 1 of Attachment 2.

We sincerely apologize for any inconvenience this error may have caused.

If you have any questions regarding this submission, please contact me at (616) 833-9896. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY



P.K. Narang, Ph.D., F.C.P.
Liaison Director
Global Regulatory Affairs

PKN:crdt

Attachments

cc: Jennifer Mercier (Desk Copy)

APPEARS THIS WAY
ON ORIGINAL

NDA 20-874 (Lunelle)

TO G. Willett, MD
S. Allen, MD, MPH

FROM S. Monroe, MD /

15

SUBJECT NDA 20-874 (Lunelle) - Phase IV Bone Mineral Density Clinical Trial

DATE 17 August 2000

Attached is another revised Protocol Summary from Pharmacia & Upjohn for the Phase IV bone mineral density (BMD) Study. In the cover letter of 9 August 2000, the sponsor "apologizes" for their "oversight" in the earlier submission. In brief, Pharmacia & Upjohn confirm that they intend to enroll 920 pts into the Lunelle arm and 460 pts into the Depo-Provera arm, with the expectation that 276 and 138 pts in the Lunelle and Depo-Provera arms, respectively, will complete 2 yrs of treatment. If they honor their commitment, this will be a very valuable study as it will be the first adequately powered prospective study of the possible adverse effects of Depo-Provera on BMD.

Pharmacia & Upjohn have clarified slightly, but not modified, their proposed statistical analysis of the BMD data and the primary endpoint. Do we need to discuss our concerns with them at this time regarding the proposed analysis/primary endpoint, or is their commitment to conducting the study adequate for now? There are no substantive study design issues other than those relating to the statistical analysis/primary endpoint. These issues were addressed in my review of the previous version of the protocol and remain unchanged.

Scott

Concur: The question commitment to study is addressed
in a memo by Dr. Hixon (10/4/00)
151
10/4/00

APPEAR THIS WAY



Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

August 9, 2000

Dr. Susan Allen, Director
Division of Reproductive and Urological Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-874
Lunelle Monthly Contraceptive Injection
(Medroxyprogesterone Acetate and
Estradiol Cypionate Injection)

General Correspondence
Corrected Version: Phase 4 Commitment

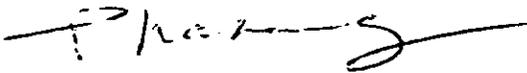
Dear Dr. Allen:

Per a telephone request from Ms. Deguia yesterday to clarify the sample size related aspects of the Phase 4 Bone Mineral density study proposal previously sent, Pharmacia and Upjohn is pleased to attach a 'corrected version' designed to assess the benefit of the added estrogen (Attachment 1). The total number of women anticipated to be enrolled is 920 for the Lunelle Monthly Contraceptive Injection (Test Arm) and 460 for the Depo-Provera Contraceptive (Reference) arms. At 2 years, we expect to have 276 and 138 evaluable women in the Test and Reference arms, respectively. We would like to bring to your attention that both "Primary End Point" and "Interim Analysis" sections have been reworded for enhanced clarity.

We apologize for the oversight at the time when this outline was last submitted and hope the Division would find this version acceptable. We look forward to sharing the "Draft Protocol" with you in due time, post-approval, to seek guidance and feedback on the adequacy of specifics. If you have any questions regarding this submission, please contact me at (616) 833-9896. Send all correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY


P.K. Narang, Ph.D., F.C.P.
Liaison Director
Global Regulatory Affairs

PKN:Imf
Attachment

cc: Ms. Eufrecina Deguia (Desk Copy)

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE <i>(Title 21, Code of Federal Regulations, 314 & 601)</i>	Form Approved: OMB No. 0910-0338 Expiration Date: April 30, 2000 See OMB Statement on page 2.
	FOR FDA USE ONLY
	APPLICATION NUMBER 20-874

APPLICANT INFORMATION

NAME OF APPLICANT Pharmacia & Upjohn Company	DATE OF SUBMISSION August 9, 2000
TELEPHONE NO. (Include Area Code) (616) 833-9896	FACSIMILE (FAX) Number (Include Area Code) (616) 833-8237
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 7000 Portage Road Kalamazoo, Michigan 49001	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Lunelle™	PROPRIETARY NAME (trade name) IF ANY	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) Medroxyprogesterone acetate and estradiol cypionate	CODE NAME (if any)	
DOSAGE FORM: Injectable Suspension	STRENGTHS: 25 mg MPA; 5 mg E ₂	ROUTE OF ADMINISTRATION: Intramuscular Injection
(PROPOSED) INDICATION(S) FOR USE: Prevention of pregnancy.		

APPLICATION INFORMATION

APPLICATION TYPE (check one)	<input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)	<input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
	<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)	

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE	<input type="checkbox"/> 505 (b) (1)	<input type="checkbox"/> 505 (b) (2)	<input type="checkbox"/> 507
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IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION (check one)	<input type="checkbox"/> ORIGINAL APPLICATION	<input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION	<input type="checkbox"/> RESUBMISSION
	<input type="checkbox"/> PRESUBMISSION	<input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT
	<input type="checkbox"/> EFFICACY SUPPLEMENT	<input type="checkbox"/> LABELING SUPPLEMENT	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT
	<input checked="" type="checkbox"/> OTHER		

REASON FOR SUBMISSION General Correspondence: Corrected Version of Phase IV Commitment

PROPOSED MARKETING STATUS (check one)	<input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx)	<input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
---------------------------------------	---	---

NUMBER OF VOLUMES SUBMITTED <u>one</u>	THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC
--	---

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

INDs _____

EF

Attn: Eufrencia DeGuia



Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

July 27, 2000

Marianne Mann, MD
Division of Reproductive & Urological Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 17B-30
5600 Fishers Lane
Rockville, MD 20857

SERIAL NO. 046

Re: IND 52,624
Lunelle® Contraceptive
Injection (Medroxyprogesterone
Acetate and Estradiol Cypionate)

Protocol Amendment
Change in Protocol

Dear Dr. Mann:

Item 6 - Protocols

Change in Protocol

Protocol 839FEH0034-0002 (Medroxyprogesterone-acetate (MPA) and estradiol-cypionate (E2C) injectable suspension: A pharmacokinetic and pharmacodynamic study after single subcutaneous administration of either 15 mg, 20 mg, or 25 mg MPA in combination with 5 mg E2C in pre-menopausal obese women. (*Protocol submitted in Serial No. 044, dated 3/17/00*).

This amendment to the protocol incorporates FDA recommendations and comments. It provides a reduction in the age limit and an extension of the follow up period to improve the quality of the information obtained from the trial. The age range will change from 18-45 years to 18-35 years (inclusive) and the follow up period will be extended for up to 120 days, if needed.

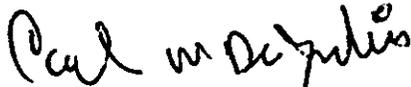
Protocol Amendment #1 provides for a reduction in the age limit and an extension of the follow up period to improve the quality of the information obtained from the trial. A copy of Amendment #1 can be found on pages 1-5.

IND _____
Page 2

If you have any questions regarding this submission, please contact me at (616) 833-9164.
Please send correspondence addressed to Unit 7025-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY



Carl M. DeJuliis, MS, RPh
Regulatory Affairs

CMD:kmv

Attachment

cc: Eufrecina DeGuia (FDA, CSO) letter and form

APPEARS THIS WAY
ON ORIGINAL

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION**

OPDRA POSTMARKETING SAFETY REVIEW

TO: Allen, M.D., Director
Division of Reproductive Drug Products (HFD-580)

FROM: Denise P. Toyer, Safety Evaluator
Division of Drug Risk Evaluation II HFD-440

OPDRA PID #
D000459

DATE REQUESTED: ASAP

REQUESTOR/Phone #: Eufrecina DeGuia, Project Manager
301-827-4260

JUL 19 2000

DATE RECEIVED: May 10, 2000

DRUG (Est): Medroxyprogesterone acetate and estradiol cypionate

NDA# 20-874

SPONSOR: Pharmacia and Upjohn

DRUG NAME (Trade): Lunelle Injection

EVENT: Thromboembolic events and other serious adverse events

Executive Summary: Lunelle Injection, a monthly injectable contraceptive, is currently under review in the Division of Reproductive and Urologic Drug Products. The clinical database contained a few reports of thromboembolic events. The trade names for the foreign equivalent of this product are: CycloProvera, CycloFem, CycloFemina, CycloGeston, and Novafem. The Division requested a review of the WHO Adverse Event Database for any serious adverse event reports including any reports of thromboembolic events. The search revealed one hundred nineteen WHO ART terms. The following terms, possibly associated with thromboembolic events, were identified: cerebrovascular disorder (3), myocardial infarction (1), pulmonary embolism (6), two phlebitis terms (5), subarachnoid hemorrhage (2), four thrombophlebitis terms (8), and three thrombosis terms (4). The entire report is attached and contains other terms that may be considered serious adverse events. The WHO report only includes a line listing of the terms and does not include any outcome or causality data and may include duplicate cases.

Reason for Request/Review:
The Division of Reproductive and Urologic Drug Products is currently reviewing a pending new drug application for Lunelle. The clinical database contained cases of thromboembolic events. This drug is currently marketed outside of the United States. DRUDP requested a search of the World Health Organization (WHO) data base for all serious adverse events including any thromboembolic cases.

Relevant Product Labeling: Not Applicable

Reference Information: Not Applicable

Search Date: May 30, 2000
June 16, 2000

Search Type(s): AERS Literature X Other: World Health Organization Database

Search Criteria: Drug Names: Medroxyprogesterone Acetate and Estradiol Cypionate

MEDDRA Terms: Not Applicable

Search Results:
WHO indicated that the combination medroxyprogesterone acetate and estradiol cypionate is not found in the WHO dictionary. WHO was unable to find any information on the following tradenames: CycloProvera, CycloFem, CycloFemina, CycloGeston, and Novafem. However, WHO searched for the following active ingredients medroxyprogesterone and estradiol and found the following products:
Divina by Neofarma, LTD of Finland (medroxyprogesterone acetate and estradiol valerate)
Klimaxil by LEO AB, of Denmark (medroxyprogesterone acetate and estradiol)
Trevina by Ercopharm, of Denmark (medroxyprogesterone and estradiol)

Discussion / Conclusions: The WHO search identified 119 WHO ART terms that included 199 reports for Divina, 23 for Klimaxil, and 2 for Trevina. The following terms, possibly associated with thromboembolic events, were identified: cerebrovascular disorder (3), myocardial infarction (1), pulmonary embolism (6), two phlebitis terms (5), subarachnoid hemorrhage (2), four thrombophlebitis terms (8), and three thrombosis terms (4). The WHO report only includes a line listing of the terms and does not include any outcome or causality data. The entire report is attached and contains other terms that may be considered as serious adverse events.

Reviewer's Signature / Date: [Signature] 7/12/00

Team Leader's Signature / Date: [Signature] 7/13/2000

Office Director Signature / Date: [Signature] 07/19/00

Attachments: WHO Report

BEST POSSIBLE COPY

Cc: NDA # 20-874

HFD 580 Division File/DeGuia/Hixon/MO-TL

HFD-440 Rodriguez/Piazza-Hepp/Toyer/Chron/Drug

~~XXXXXXXXXX~~

Electronic File Name: Lunelle.Thromboembolic.06-00-00.Toyer.D000459.doc

APPEARS THIS WAY
ON ORIGINAL

|S|
= entered
in DFS
8/2/00

Teleconference Minutes

Date: June 12, 2000

Time: 1:00 – 1:30 PM

Location: Room 18B-09

NDA 20-874

Drug Name: Lunelle™ Monthly Contraceptive Injection
(medroxyprogesterone acetate and estradiol cypionate
injectable suspension)

Indication: Prevention of pregnancy

Sponsor: Pharmacia & Upjohn

Type of Meeting: Guidance (Clinical)

Meeting Chair: Dr. Dena Hixon

External Participant Lead: Dr. P.K. Narang

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:

Eufrecina DeGuia - Regulatory Project Manager, DRUDP (HFD-580)

Dena Hixon, M.D. – Medical Officer, DRUDP (HFD-580)

Scott Monroe, M.D. – Medical Officer, DRUDP (HFD-580)

External Participants:

Charles Wajszczuk – Clinical Development

Carl DeJuliis – Global Regulatory Affairs

Maureen McConnell – Biostatistics

Cynthia Greenwald – Biostatistics

P.K. Narang, Ph.D. – Global Regulatory Affairs

Meeting Objectives: To discuss the status of the review and the issues regarding Pharmacia & Upjohn's submission on the re-analysis of bleeding pattern.

Background: On September 26, 1997, Pharmacia and Upjohn submitted an original NDA seeking approval for marketing the product in the United States. The application revealed clinical deficiencies that resulted in a Non-Approval decision on September 25, 1998. A complete response to this action was submitted on April 15, 1999 but found to be inadequate to support approval due to unresolved Chemistry and labeling deficiencies. The application was issued an Approvable (AE) action on October 15, 1999. An amendment was submitted on April 6, 2000 which constituted another complete response to the last AE action. This application is on a six-month review clock.

Decisions reached:

- to demonstrate the benefit of adding estrogen; a revised Protocol Summary should be submitted for a BMD study with Lunelle and either a single comparator, Depo-Provera (150 mg every three months), or a three-arms study with Depo-Provera and 25 mg MPA monthly as comparators; sponsor may include bone resorption markers (not required) in addition to DEXA scans of the lumbar spine and hip (required); this revised summary should be submitted prior to action on the application

Meeting Minutes

Page 2

- as previously stated, final protocol should be submitted within six months of action and it should state when the study will be initiated and when the results are expected
- a rationale should be included in the BMD protocol justification for the selection of a one-year primary endpoint instead of a two-year endpoint
- BMD study will take precedence to the other suggested Phase 4 commitment
- the submitted re-analysis of bleeding pattern will not change any of the labeling suggestions already made by the Division
- the sponsor may submit proposed labeling to advise clinicians of expected bleeding patterns

Action Items:

- meeting minutes will be sent to the sponsor in 30 days

ES/

ES/

7/11/00

Signature, minutes preparer

7/11/00

Concurrence, Chair

NOTE: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcome.

cc:

NDA Arch:

HFD-580/DeGuia/TRumble

HFD-580/DHixon, SMonroe

drafted: DeGuia/06.20.00

Concurrences: TRumble06.26.00/SMonroe07.05.00/DHixon07.10.00

Final: EDeGuia07.10.00

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL



Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

June 7, 2000

Ms. Janine Best
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



RE: **NDA 20-874**
Lunelle™ Monthly Contraceptive Injection
(Medroxyprogesterone acetate and Estradiol cypionate
Injectable Suspension)

GENERAL CORRESPONDENCE
INTERNATIONAL LABELING

NEW CORRESP
NC

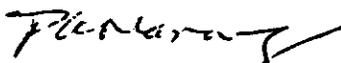
Dear Ms. Best:

As I indicated to you over the phone this afternoon, after our submission on the above topic had left earlier this morning stating that no English version was available, we were able to get hold of an English version of labeling for Cyclofem (product marketed in Indonesia) (See Attachment A). This product is under the license of Concept Foundation in Thailand. Pharmacia and Upjohn (P&U) does not currently market this product in any international markets.

We hope that you and the Division would find this labeling information useful. If you have any questions regarding this submission, please contact me at (616) 833-9896. Send all correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY


P.K. Narang, Ph.D., F.C.P.
Director
Global Regulatory Affairs

PKN:lmf

REVIEW'S COMPLETED
DATE: 6/16/00
BY: [Signature]
REVIEWER'S NAME: [Signature]
DATE: [Blank]
REVIEWER'S NAME: [Blank]

Reviewed
6/16/00
BKH

BEST POSSIBLE COPY



Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

June 6, 2000

Ms. Janine Best
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 20-874
Lunelle™ Monthly Contraceptive Injection
(Medroxyprogesterone acetate and Estradiol cypionate
Injectable Suspension)

GENERAL CORRESPONDENCE
INTERNATIONAL LABELING

NEW CORRESP
NC

Dear Ms. Best

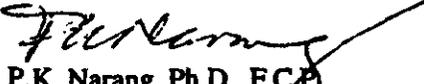
Ms. Eufrecina Deguia (Project Manager, DRUDP) voice mail message of June 2, 2000 forwarded a request from the Division for providing international labeling of LUNELLE Monthly Contraceptive Injection. Pharmacia and Upjohn (P&U) does not currently market this product in any international markets.

Medroxyprogesterone acetate (25mg) and Estradiol cypionate (5 mg) Injectable Suspension (CYCLOFEM and CYCLOFEMINA) is marketed in several countries (i.e. Brazil, Chile, Mexico, Indonesia, etc) by other companies. Recent P&U's attempts to procure an English version of a label have not been successful. Therefore, we are unable to provide you with any International Labeling at this time. Per Ms. Deguia's instructions, this submission is being sent to your attention.

If you have any questions regarding this submission, please contact me at (616) 833-9896. Send all correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY


P.K. Narang, Ph.D., F.C.P.
Global Regulatory Affairs Director

PKN:kmv

REVIEWS COMPLETED
DISPOSITION
<input type="checkbox"/> LETTER <input checked="" type="checkbox"/> FINAL <input type="checkbox"/> MEMO
ED 6/13/00
DATE
CSG INITIALS

BEST POSSIBLE COPY

DeGuis
entered in
DFS
8/2/00

Meeting Minutes

Date: June 2, 2000

Time: 11:00 AM – 12:00 PM

Location: Conference Room "O"

NDA 20-874

Drug Name: Lunelle™ Monthly Contraceptive Injection
(medroxyprogesterone acetate and estradiol cypionate
injectable suspension)

Indication: Prevention of pregnancy
Cartridge

Sponsor: Pharmacia & Upjohn

Type of Meeting: Status (Clinical)

Meeting Chair: Dr. Susan Allen

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:

Susan Allen, M.D., M.P.H., Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Florence Houn, M.D., M.P.H. - Office Director, ODE III

Terri Rumble, Chief, Regulatory Project Management Staff, DRUDP (HFD-580)

Eufrecina DeGuia, Regulatory Project Manager, DRUDP (HFD-580)

Dena Hixon, M.D. – Medical Officer, DRUDP (HFD-580)

Scott Monroe, M.D. – Medical Officer, DRUDP (HFD-580)

Dhruba Chatterjee, Ph.D. – Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)

Meeting Objectives: To discuss the status of the review and the issues regarding Pharmacia & Upjohn's submission on the re-analysis of the bleeding pattern.

Background: On September 26, 1997, Pharmacia and Upjohn submitted an original NDA seeking approval for marketing the product in the United States. The application revealed clinical deficiencies that resulted in a Non-Approval decision on September 25, 1998. A complete response to this action was submitted on April 15, 1999 but found to be inadequate to support approval due to unresolved Chemistry and labeling deficiencies. The application was issued an Approvable (AE) action on October 15, 1999. An amendment was submitted on April 6, 2000 which constituted another complete response to the last AE action. This application is on a six-month review clock.

Discussion Points:

- the significant amount of weight gain noted in study subjects could be of concern to potential users and should be addressed in labeling
- the re-analysis of bleeding pattern does not support any changes from previous labeling recommendations
 - clinically undesirable bleeding patterns by Belsey's criteria were reported (>60%) compared with Ortho-Novum (>40%)
 - the sponsor proposes a "normal or clinically acceptable" withdrawal menstrual bleeding period from Day 18-31 post dosing; the Division does not consider this to be normal or acceptable

- estrogen was added to the DMPA product to produce a bleeding pattern that would more closely mimic a normal cycle, hoping to show that monthly injections would result in monthly uterine bleeding similar to that found in naturally cycling women and that induced pharmacologically in women using combined oral contraceptives; the proposal did not support this assertion by the sponsor so Phase IV studies may be needed to further justify the estrogen component
 - another theoretical advantage of adding estrogen to DMPA is that it might contribute to a positive effect on bone (i.e., less or no bone loss as reported for DMPA alone)
- inhibition of ovulation is a result of the MPA component and the addition of estrogen may inhibit follicular activity
- early studies submitted with the original NDA do show a faster return to ovulation with the combination product than with MPA alone
- with regards to the decreased incidence of amenorrhea, it is not clear whether this is due to the estrogen component of Lunelle or due to the monthly administration of the combined product compared to the three-month injectable formulation that contains 150 mg of MPA

Decisions reached:

- the rate of weight change should be addressed in the PRECAUTION section of the label; it should be moved up to #2 under the General Precaution of the PPI ; in addition, it should be in a "table" format not "text" format
- a revised Protocol Summary for BMD studies with a comparator should be submitted
- a final protocol for the BMD studies should be submitted within six months of action and should state when the study will be initiated and when the results are expected to be reported to the Division
- a rationale should be included in the justification for the selection of a one-year primary endpoint instead of two-year endpoint
- the submitted re-analysis of bleeding pattern will not change any of the labeling suggestions previously made by the Division
- the Division did not see any proposal for bleeding pattern changes in labeling; the sponsor may submit proposed labeling to advise clinicians of expected bleeding patterns
- the sponsor will be asked to commit to Phase 4 studies on BMD
- the 1997 WHO study will be reviewed by the Division including the PK/PD data on return to ovulation of women after treatment with MPA alone and after treatment with MPA + estrogen; if data is not adequate then additional Phase IV study may be required

Action Items:

- review will continue as scheduled

/S/

7/10/00

Signature, minutes preparer

/S/

Concurrence, Chair

mm

APPEARS THIS WAY
ON ORIGINAL

Meeting Minutes

Page 3

cc:

NDA Arch:

HFD-580/DeGuia/TRumble

HFD-580/TRumble/SAllen/SMonroe/DHixon,DChatterjee/FHoun

drafted: DeGuia/06.19.00

Concurrences:DHixon06.19.00/TRumble06.26.00/DChatterjee06.27.00/SMonroe/SAllen07.10.00

final: EDeGuia07.10.00

MEETING MINUTES

**APPEARS THIS WAY
ON ORIGINAL**



Pharmacia & Upjohn

Global Regulatory Affairs
David W. Johnson, Associate Director
Global Promotion & Labeling
0632-298-130
Telephone No. (616) 833-4395
Facsimile No. (616) 833-8632

May 31, 2000

Lisa Stockbridge, Ph.D.
Division of Drug Marketing,
Advertising, and Communications, HFD-42
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-874
LUNELLE™ Contraceptive Injection (medroxyprogesterone acetate and estradiol
cypionate contraceptive injection)

Dear Dr. Stockbridge:

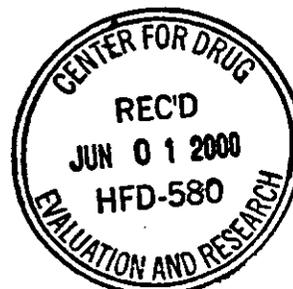
As discussed in our telephone conversation on May 31, 2000, Pharmacia & Upjohn is formally withdrawing the submission to DDMAC dated January 14, 2000, in which we requested review of proposed introductory promotional materials for LUNELLE Contraceptive Injection. We are planning to resubmit these materials for your review and comment after approval of the NDA and finalization of the labeling.

In the meantime, please contact me at (616) 833-4395 if you have any questions.

Sincerely,

David W. Johnson, R.Ph.
Associate Director
Global Promotion & Labeling

cc: Jennifer Mercier, B.S.





Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

May 15, 2000

Dena Hixon, M.D.
Division of Reproductive and Urological Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

**RE: NDA 20-874
Lunelle™ Monthly Contraceptive Injection
(Medroxyprogesterone Acetate and
Estradiol Cypionate Injection)**

DESK COPY

Dear Dr. Hixon:

Per Ms. Jennifer Mercier's recommendation, Pharmacia and Upjohn is sharing this Desk Copy of a briefing document dealing with what we believe is a more scientifically appropriate and robust analysis of the 'menstrual bleeding' data following the use of the Lunelle 'Monthly' Contraceptive Injection. Our ultimate intent, as you may envision, is to possibly explore its relevance and have an opportunity to revisit components of the current proposed labeling impacted by the new analysis.

Since the finalization of the US pivotal trial study report (/0004), there has been a general consensus among those working with this project within the company and many external OB/GYN experts regarding the relevance of the 'per-protocol analysis' submitted to you in our Amendment # 001 (April 15, 1999). This primarily reflects the use of Belsey's methodology, designed for the assessment of bleeding patterns for 'longer acting' products, as applied to a monthly injectable contraceptive. Since our original submission was based on the WHO trials data, which employed similar methodology for analyses, it was deemed prudent to apply same definitions to compare the data in these trials.

There are three primary reasons why we undertook this effort during the last few months:

1. Clinical development planning for the registration of a subcutaneous (SQ) dosing route for a 'new' combination product further optimizing the return to ovulation and hopefully, menstrual bleeding experience of the end-user. This necessitated an assessment of the merits and adequacy of the Belsy's approach to 'bleeding' data for a product with a once monthly cyclic dosing. Our intent is to use this monthly methodology in the Phase I/II study submitted with our new IND for the SQ route (May 1, 2000).
2. Lack of a monthly injectable reference product for guidance on an accepted approach to analysis of such data.
3. Feedback and discussions with OB/GYN experts regarding the relevance (e.g., in terms of familiarity and improving the understanding/counseling for both physician and women) of the bleeding information in the current proposed labeling for Lunelle Monthly Contraceptive Injection.

In this new analysis, we are providing an approach more suited for handling bleeding data for this product consistent with a 'monthly contraceptive injection'. Establishment of windows for variables borrows from the experience/approach employed by products with similar monthly cyclic regimens.

We recognize the possibility that the Division may deem any subsequent submission, 'clinically significant new data' (per 21 CFR 314.60 (a)). Given the ongoing review of the NDA, P&U would be very pleased if you could provide us with some feedback in a week on the feasibility of furthering this approach to assist us in charting the next steps.

If there are any questions, please do not hesitate to call me at 616 833 9896.

Best regards!

Sincerely,

PHARMACIA & UPJOHN COMPANY


P.K. Narang, Ph.D., F.C.P.
Director

APPEARS THIS WAY
ON ORIGINAL

PKN:lmf

Attachment

DIF

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 4/26/00

DUE DATE: 5/19/00

OPDRA CONSULT #: 00-0132

TO:

Susan Allen, M.D.
Acting Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH:

Jennifer Mercier
Project Manager
HFD-580

PRODUCT NAME:

Lunelle
(medroxyprogesterone acetate and
estradiol cypionate injectable
suspension)
NDA #: 20-874

MANUFACTURER: Pharmacia and Upjohn

SAFETY EVALUATOR: Peter Tam, R.Ph.

OPDRA RECOMMENDATION:

OPDRA has no objections to the use of the proprietary name, Lunelle. See the checked box below.

FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW

This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW

OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

FOR PRIORITY 6 MONTH REVIEWS

OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

151
Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

181
5/11/2000
Peter Honig, M.D.
Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 5/4/00

NDA#: 20-874

NAME OF DRUG: Lunelle
(medroxyprogesterone acetate and estradiol cypionate
injectable suspension)

NDA HOLDER: Pharmacia and Upjohn

I. INTRODUCTION:

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580) on April 26, 2000, to review the proposed proprietary drug name, Lunelle, in regard to potential name confusion with existing proprietary/generic drug names. The goal date is June 7, 2000.

The Labeling and Nomenclature Committee (LNC) previously reviewed the proposed proprietary name, Lunelle. LNC found the proposed proprietary name, Lunelle, acceptable.

PRODUCT INFORMATION

Lunelle contains medroxyprogesterone acetate and estradiol cypionate as its active ingredients. It is available as a 0.5 mL aqueous suspension and contains 25 mg medroxyprogesterone acetate and 5 mg estradiol cypionate. When Lunelle injection is administered at the recommended dose to women every month, it inhibits the secretion of gonadotropins, which, in turn, prevents follicular maturation and ovulation. Although the primary mechanism of this action is inhibition of ovulation, other possible mechanisms of action include thickening and a reduction in volume of cervical mucus (which decrease sperm penetration) and thickening of the endometrium (which may reduce the likelihood of implantation).

Lunelle, Monthly Contraceptive Injection, is effective for contraception during the first cycle of use when administered as recommended. The recommended dose of Lunelle Monthly Contraceptive Injection is 0.5 mL administered by intramuscular injection, into the deltoid, gluteus maximus, or anterior thigh. Second and subsequent injections is monthly (28-30 days) after the previous injection, not to exceed 33 days.

Lunelle Monthly Contraceptive Injection will be available in a vial containing enough product to deliver 0.5 mL for single-dose administration.

II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts^{1,2,3} as well as several FDA databases⁴ for existing drug names which sound alike or look alike to Lunelle to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁵. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

The expert panel consists of members of OPDRA's medication error Safety Evaluator Staff and a representative from the Division of Drug Marketing, Advertising and Communications (DDMAC).

1. The expert panel expressed some concerns with the existing approved product, Luminal Injection and a few other potential names such as Activella, Vivelle, Ludiomil, Lamisil and Lexxel. However, considering the limited use and distribution of this proposed product, Lunelle, the panel did not feel the name had much safety risk potential for confusion.

Drug Name	Drug Name, Strength, Dosage Form	Dose Range	Comments
Luminal	Injectable 1 mL amp, phenobarbital 130mg/ml	30-320 mg in divided doses IM or IV	*SA/LA
Activella	Tablet containing 1 mg estradiol and 0.5 mg norethindrone	One tablet daily	*SA
Vivelle	Transdermal estradiol patch, available in 0.05/0.75/0.1/0.375 ug	One patch daily	*SA
Ludiomil	Tablet-25/50/75 mg, maprotiline	75-150 mg/day	*SA

¹ MICROMEDEX Healthcare Intranet Series, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc).

² American Drug Index, online version, Facts and Comparisons, St. Louis, MO.

³ Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

⁴ Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

⁵ WWW location <http://www.uspto.gov/tmdb/index.html>.

Lamisil	Tablet- terbinafine	250 mg/day for 6-12 weeks	*SA
Lexxel	Extended-release tablets, combination of enalapril + felodipine	One tablet daily	*SA

*SA = Sound-alike

*LA = Look-alike

The panel concluded that the above listed drugs and Lunelle pose no significant safety risk, and therefore, the proprietary name, Lunelle, is not objectionable.

2. DDMA~~C~~ - no objections

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ON ORIGINAL

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B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

These studies were conducted by OPDRA and involved 94 health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Lunelle with other drug names due to the similarity in handwriting and verbal pronunciation of the name. Inpatient order and outpatient prescriptions were written, each consisting of (known/unknown) drug products and a prescription for Lunelle (see below). These prescriptions were scanned into a computer and were then delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

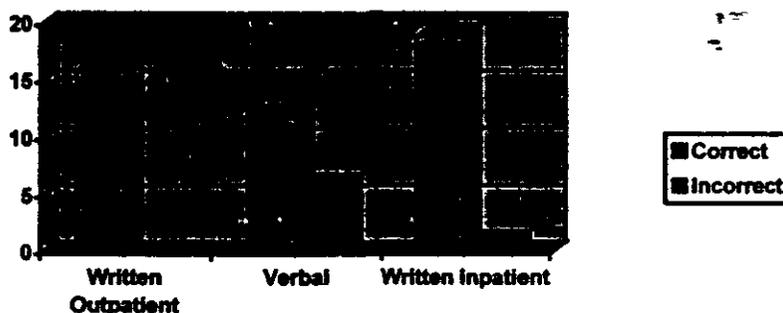
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p><u>Outpatient RX:</u> Lunelle 0.5 mL IM Sig: As directed</p>	<p>Lunelle 0.5 mL IM Sig: As directed</p>
<p><u>Inpatient RX:</u> To receive Lunelle 0.5 mL IM x 1 on April 29.</p>	

2. Results:

The results are summarized in Table I.

Table I

<u>Study</u>	<u># of Participants</u>	<u># of Responses (%)</u>	<u>Correctly Interpreted</u>	<u>Incorrectly Interpreted</u>
Written Outpatient	32	16 (50%)	16	0
Verbal	31	18 (58%)	12	6
Written Inpatient	31	20 (65%)	19	1
Total	94	54 (57%)	47 (87%)	7 (13%)



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Eighty-seven percent of the participants responded with the correct name, Lunelle. The incorrect written and verbal responses are as follows in Table II.

Table II

	<u>Incorrectly Interpreted</u>
Written Inpatient	Lunette
Verbal	<u>Phonetic Variable Responses</u>
	Linell
	Lemel (3)
	Lounel
	Loenil

C. SAFETY EVALUATOR RISK ASSESSMENT

A number of product names were identified in the expert panel discussion that were thought to be similar to Lunelle. Luminal (phenobarbital) injection was identified to have potential for confusion with Lunelle due to its sound-alike and look-alike similarities. Both drugs are injectable products, but Lunelle is indicated for pregnancy prevention while Luminal is used for sedative and anti-convulsion therapy. Lunelle is recommended for IM use and so is Luminal (IM or IV). Despite these similarities, Lunelle and Luminal differ in terms of dose, strength, dosing interval and other factors such as to how and when the drug will be used as well as the patient population that will use this drug.

The results of the verbal prescription study indicates that twelve (out of eighteen) participants interpreted Lunelle correctly. In the written outpatient and inpatient studies, sixteen (out of sixteen) and nineteen (out of twenty) participants interpreted the proposed name, Lunelle correctly. Many of the incorrect responses were misspelled/phonetic variation of the drug name. Finally, in all three studies, we did not uncover any overlapping existing drug names. Because of the size of the study, this does not provide persuasive evidence that an error might not occur when exposed to the general population.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

We have no comments.

IV. RECOMMENDATIONS:

OPDRA has no objections to the use of the proprietary name, Lunelle.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Peter Tam at 301-827-3241.

/S/

5/10/00

Peter Tam, R.Ph.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/

5/11/00

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

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ON ORIGINAL

CC:

NDA - 20-874

Office Files

HFD-580; Jennifer Mercier, Project Manager, DRUDP

HFD-580; Heidi M. Jolson, M.D., Division Director, DRUDP

HFD-042; Patricia Staub, Regulatory Review Officer, DDMAC (Electronic Only)

HFD-440; Debbie Boxwell, Safety Evaluator, DDREII, OPDRA

HFD-400; Jerry Phillips, Associate Director, OPDRA

HFD-400; Peter Honig, Director, OPDRA (Electronic Only)

HFD-002; Murray Lumpkin, Deputy Center Director for Review Management (Electronic Only)

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ON ORIGINAL

Appendix A
(Trademark Review by OPDRA)

**APPEARS THIS WAY
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Meeting Minutes

Date: May 9, 2000

Time: 12:00-12:45 pm

Location: Parklawn; 17B-43

NDA 20-874

Drug: Lunelle™ (medroxyprogesterone acetate and estradiol cypionate)

Indication: Contraception

Sponsor: Pharmacia and Upjohn

Type of Meeting: Status/Label Meeting

Meeting Chair: Dr. Susan Allen, M.D.

Meeting Recorder: Jeanine Best

FDA Attendees:

Florence Houn, M.D., M.P.H., Director, Office of Drug Evaluation III (ODE III, HFD-103)

Susan Allen, M.D., M.P.H., Acting Director, Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)

Dena Hixon, M.D., Acting Team Leader, DRUDP (HFD-580)

Scott Monroe, M.D., Medical Officer, DRUDP (HFD-580)

David Lin, Ph.D., Chemist, Division Of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

DJ Chatterjee, Ph.D., Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics, (OCPB) @ DRUDP (HFD-580)

Terri Rumble, B.S.N., Chief, Project Management Staff, DRUDP (HFD-580)

Jeanine Best, M.S.N., R.N., Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss status of reviews, labeling issues, and approvability of this NDA.

Background: This NDA was originally submitted on September 25, 1997 and received a not approvable action on September 25, 1998. The sponsor then submitted this application on April 15, 1999 and received an approvable action on October 15, 1999. The sponsor submitted this resubmission dated April 6, 2000 as complete response to the action letter.

Discussion:

Biopharmaceutics:

- no new data submitted
- label will be reviewed for any changes to PK section since last review
- memo will be written if labeling issues are resolved

Chemistry:

- inspection of facilities are acceptable
- carton and packaging labels received; appear acceptable
- OPDRA Tradename consult is pending

Clinical:

- clinical safety update data and summary appear acceptable
- review should be complete by end of next week
- labeling:
 - no suggestion of benefit from estrogen component to be allowed in label
 - Bone Mineral Density (BMD) statement is otherwise identical to that of Depo-Provera label and should not be removed from this label; BMD loss is a potential safety issue
 - sponsor indicated irregular bleeding occurs during early cycles and may continue throughout usage of product
 - **ADVERSE REACTIONS** section is similar to that appearing in the Estrostep® label; no issue found with the differences
- Regulatory issue; this product may not meet the criteria for combination drug rule; re-evaluate whether sponsor demonstrated benefit of estrogen component; improvement in bleeding patterns not shown; sponsor needs to describe rationale for meeting the drug combination rule and Division will evaluate and determine acceptability of their response
- formulation of drug product can be justified; product has been used for many years in several other countries; during last review cycle, product determined to be effective as a contraceptive; with no safety issues identified
- sponsor reported that they would send protocol for Phase 4 studies within six months of approval; they are proposing a non-comparator BMD study with 150 new users, with follow-up for one year with possible extension to two years; Division will provide recommendations for Phase 4 study designs

Decisions made:

- none at this time

Unresolved decisions:

- NDA approvability in light of regulatory issues related to combination drug rule

Action Items:

- D. Hixon and S. Monroe to work on wording on BMD statement in the label
- D. Hixon to contact OPDRA to check for AE's, and especially VTE's in the WHO database for foreign postmarketing reports
- J. Best to obtain 1972 DESI Notice in the Federal Register regarding the effectiveness of estrogen and progestin in oral contraceptives
- The Division will continue to address justification of the estrogen component
- The Division will request the sponsor to submit appropriate final Phase 4 protocols prior to approval

/S/

Minutes Preparer

/S/

Concurrence, Chair

MMO
5/16/00

cc:

Original IND

HFD-580/DivFile

HFD-580/PM/Best/Mercier

HFD-580/Allen/Hixon/Monroe/Chatterjee/Lin/Rumble

HFD-103/Houn

drafted: JAB/May 9, 2000

concurrence: Chatterjee,05.09.00/Hixon,05.11.00/Rumble,05.11.00/Allen, 05.12.00

final: May 16, 2000

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL



Pharmacia & Upjohn

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA
Telephone: (616) 833-4000

May 2, 2000

DESK COPY

Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
Attention: Susan Allen, M.D.



Re: **NDA 20-874**
Lunelle™ Monthly Contraceptive Injection
(Medroxyprogesterone acetate and Estradiol cypionate
Injectable Suspension)

General Correspondence
Labeling: Non-Insert

Dear Dr. Allen

On May 1, 2000, Ms. Jennifer Mercier from your Division requested that Pharmacia and Upjohn (PNU) resubmit the "non-insert labeling" to NDA 20-874. PNU is pleased to provide the following copies (1 of each):

1. Vial
2. Sample Vial
3. 1 Sample Carton
4. 3, 25, and 1 pack cartons

Back in October of 1999, the FDA found the above "non-insert labeling" to be acceptable.

APPEARS THIS
ON ORIGINAL

NDA 20-874

Page 2

If you have any questions regarding this submission, please contact me at (616) 833-9896. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY



P.K. Narang, Ph.D., F.C.P.

Director

PKN:SEH

Attachments

cc: Jennifer Mercier (Two Desk Copies)

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Meeting Minutes

Date: April 26, 2000 **Time:** 9:00 – 10:00 AM

Location: Parklawn; 17B-43

NDA 20-874

Drug: Lunelle™(medroxyprogesterone acetate and estradiol cypionate)

Indication: Contraception

Sponsor: Pharmacia and Upjohn

Type of Meeting: Status and Review Meeting

Meeting Chair: Susan Allen, M.D.

Meeting Recorder: Jennifer Mercier, B.S.

FDA Attendees:

Florence Houn, M.D. – Director, Office of Drug Evaluation III (ODEIII; HFD-103)

Susan Allen, M.D. – Acting Director, Division of Reproductive and Urologic Drug Products (DRUDP); HFD-580

Marianne Mann, M.D. – Deputy Director, DRUDP (HFD-580)

Dena Hixon, M.D. – Acting Team Leader, DRUDP (HFD-580)

Scott Monroe, M.D. – Medical Officer, DRUDP (HFD-580)

David Lin, Ph.D. – Chemist, Division of New Drug Chemistry II (DNDCII) @ DRUDP (HFD-580)

Jeanine Best, M.S.N., R.N. – Regulatory Project Manager, DRUDP (HFD-580)

Terri Rumble – Chief, Project Management Staff, DRUDP (HFD-580)

Jennifer Mercier, B.S. – Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss the completeness and acceptability of this resubmission.

Background: This NDA was originally submitted on September 25, 1997 and received a not approval action on September 25, 1998. The sponsor then resubmitted this application on April 15, 1999 and received an approvable action on October 15, 1999. This resubmission dated April 6, 2000 was submitted as a complete response by the sponsor.

Decisions made:

Clinical

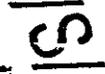
- this response to the AE letter appears complete
- the sponsor proposed minor labeling changes from the proposed label sent to them with the approvable letter dated October 15, 1999
- the sponsor has submitted the Phase 4 study summaries and the Division will review them and provide any comments to the sponsor
- this application is being reviewed as a Class 2 resubmission because the sponsor submitted additional clinical data requiring review for the label

Chemistry

- application is considered complete for resubmission review
- Lunelle™ Once A Month Contraceptive will need another tradename review by OPDRA
- the inspection has been requested for the sterile product facility; EES has listed the site as approved

Action Items:

- send sponsor acknowledgement letter of complete response as a Class 2 resubmission with 6 month review clock (complete); the Division will try for completion in two months
- send consultation to OPDRA for tradename review (complete)


Minutes Preparer


Concurrence, Chair 5/8/00

APPEARS THIS WAY
ON ORIGINAL

cc:

Original NDA

HFD-580/DivFile

HFD-580/PM/Rumble/Pauls/Mercier

HFD-580/Allen/Mann/Hixon/Monroe/Lin/Rhee/Parekh/Chatterjee/Best

drafted: April 27, 2000

concurrence:

Rumble4.28.00/Mann4.28.00/Best4.28.00/Hixon5.1.00/Allen4.28.00/Houn4.28.00/Lin5.04.00

final: JAB/May 8, 2000

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

D-File

NDA 20-874

Pharmacia & Upjohn
Attention: P.K. Narang, Ph.D., F.C.P.
Liaison Director
Global Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 49001-0199

APR 26 2000

Dear Dr. Narang:

We acknowledge receipt on April 7, 2000 of your April 6, 2000 resubmission to your new drug application (NDA) for LUNELLE™ Monthly Contraceptive Injection (medroxyprogesterone acetate and estradiol cypionate injection).

This resubmission contains additional chemistry and clinical information submitted in response to our October 15, 1999 action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is October 7, 2000.

If you have any questions, call Jennifer Mercier, B.S., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

TS

4/26/00

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:

Archival NDA 20-874

HFD-580/Div. Files

HFD-580/J.Mercier

HFD-580/Allen/Mann/Hixon/Monroe/Rhee/Lin/Parekh/Chatterjee

DISTRICT OFFICE

Drafted by: JM/April 26, 2000

Initialed by: 

final:

CLASS 2 RESUBMISSION ACKNOWLEDGEMENT (AC)

(DDR: Update the user fee goal date based on the class of resubmission.)

**APPEARS THIS WAY
ON ORIGINAL**



Pharmacia & Upjohn

ORIGINAL

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

ORIG AMENDMENT

AZ

April 6, 2000

Dr. Lisa Rarick, Director
Division of Reproductive and Urological Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 20-874
Lunelle Monthly Contraceptive Injection
(Medroxyprogesterone Acetate and
Estradiol Cypionate Injection)

Amendment 002
Response to October 15, 1999
Approvable Letter

Dear Dr. Rarick:

Per 21 CFR 314.60, Pharmacia and Upjohn (P&U) is pleased to provide this amendment, in anticipation of what we hope would constitute a 'complete response' to the letter received October 15, 1999 for the NDA 20-874 for Lunelle Monthly Contraceptive Injection.

Our response to issues agency wished for us to address is summarized below:

▪ **Manufacturing Deficiencies at the [redacted] Plant - [redacted]**
P&U is amending this application to permit the manufacturing of the Lunelle Monthly Contraceptive Injection in our recently upgraded [redacted] production facilities in Kalamazoo, MI. All relevant information pertaining to [redacted] validation' supporting the manufacturing of Lunelle Monthly Contraceptive Injection is described in P&U's [redacted] Facility Upgrade" Type V DMF (DMF [redacted]) submitted on March 27, 2000. We understand that Dr. Peter Cooney (Office of New Drugs Chemistry) found the [redacted] validation package acceptable. In addition the Detroit Office staff has indicated that P&U is free to manufacture and release products from this facility.

Note: the product formulation, manufacturing processes, specifications, and packaging remain unchanged.

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> MEMO
CSO INITIALS	DATE

▪ **Revised Labeling: Physician and Patient Inserts**

On October 15, 1999, P&U also received from the Division proposed labeling suggestions and recommendations for both Physician and Patient Insert (attached to the 'Approvable Letter') for LUNELLE Monthly Contraceptive Injection. The letter requested P&U to submit revised 'draft' labeling as a part of this amendment. The following 'Labeling' files are provided (Attachment 1):

1. Physician Insert (Revised: P&U-strikeout version dated 3/31/2000)
2. Patient Insert (Revised: P&U: strikeout version dated 3/31/2000)

Both WORD and the Adobe Acrobat (.pdf) versions are provided on a CD-ROM as well.

▪ **Phase IV Commitment: Study Proposals**

After much consideration/debate of the underlying dose/regimen issues of comparing this product with an approved product containing MPA alone or controlling for the MPA dose, P&U proposes two Phase IV studies with Lunelle Monthly Contraceptive Injection to establish the benefit of added estrogen. "Draft summaries" of these studies detailing key design facets are provided (Attachment 2). As noted in our October 13, 1999 General Correspondence, we commit to seek Division's guidance within six months from the date of the approval prior to finalizing specific protocols and agreement before initiation of these studies.

▪ **Safety Update**

Our previous safety update, submitted in August 1999 to this NDA 20-874 included data from Protocol M/5415/0011 (data cutoff May 31, 1999) and from a discontinued study (Protocol M/5415/0009). A Phase I (IV) type of study, (Protocol Z/5415/0012) comparing ovarian follicular activity between Lunelle Monthly Contraceptive Injection and an oral contraceptive was also referenced.

As requested, a new safety update is provided (Attachment 3). This safety report updates the information previously reported in NDA 20-874 and subsequent amendments more thoroughly by providing an integrated summary of the data from Protocols 0004 and 0011 (cut-off date February 8, 2000. Also included is safety gleaned from published sources over the period (May 31, 1999 (cutoff date for the previous safety update report) through February 8, 2000). Since, Protocols M/5415/0009 and Z/5415/0012 provided no new data over this period, we have not discussed these any further. However, final study reports for each are provided (Appendix 3; Safety Update).

Appendix 4 (under Attachment 3 provides case report forms (CRFs) in electronic format (as .pdf files) for all women who discontinued from protocol 11 due to adverse events. The electronic component, using CD-ROM as transport media, conforms to the CDER guidance and consists of approximately 5 MB of information. A copy of this cover letter, Form 356H and the Table of Contents are included on the CD-ROM.

All enclosed transport media have been checked using VirusScan NT 4.0.3 and deemed 'virus free'.

Given the stage at which our discussions were in mid-October 1999, P&U anxiously looks forward to having a quick review of this amendment. Should there be any questions regarding this submission, please call me at 616-833-9896. Send all correspondence to 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY



P.K. Narang, Ph.D., F.C.P.
Liaison Director
Global Regulatory Affairs

PKN:kmv

cc: Ms. Jennifer Mercier (Project Manager)
Copy of the letter+356H

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL



Pharmacia & Upjohn

NEW CORRESP

Pharmacia & Upjohn
7000 PoPage Road
Kalamazoo, MI 49001-0199
USA
Telephone: (616) 833-4000

OCT 17 1999

Office of:
P.K. Narang, Ph.D., F.C.P.
Liaison Director, New Drugs
Global Regulatory Affairs

Telephone No. (616) 833-9896
Facsimile No. (616) 833-8237

October 25, 99

Lisa Rarick, M.D.
Division of Reproductive and Urological Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

OCT 17 1999

RE: NDA 20-874
LUNELLE™ Monthly Contraceptive Injection
(Medroxyprogesterone Acetate and
Estradiol Cypionate Injectable Suspension)

General Correspondence
Response to FDA Action Letter (October 15, 1999)

Dear Dr. Rarick

In response to the NDA 'approvable action letter' dated October 15, 1999, per available options under 21 CFR 314.110(a), Pharmacia and Upjohn (P&U) would like to notify you of its intent to file an amendment to the above NDA to resolve the noted issues.

We anticipate this amendment to the NDA to provide a 'complete response' to the action letter, and look forward to keeping the division apprised of our progress.

If you have any questions regarding this submission, please contact P.K. Narang at (616) 833-9896. Please send any correspondence to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN

P.K. Narang, Ph.D., F.C.P.
Liaison Director, Women's Health
Global Regulatory Affairs

PKN:SEH

cc: Ms. Jennifer Mercier (FAX Letter : 301 827 4267)

REVIEWS COMPLETED
CSO ACTION
LETTER <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
CSO INITIALS <i>PK</i> DATE <i>10/11/99</i>

*moved
Oct
11/01/99*

BEST POSSIBLE COPY

Pharmacia & Upjohn

Regulatory Affairs

Director, Regulatory Liaison, New Drugs

For operator assistance call 616-833-6966

To: Ms. Jennifer Mercier, FDA	
Fax No: 301-827-4267	
Subject: Lunelle, (NDA # 20-874)	
Copies:	
From: P. K. Narang 0635-298-101	
Tel No: 616-833-9896	Fax No: 616-833-0409
Date: 10-15-99	Pages (including this one): 3

Dear Jennifer:**As per our phone conversation this morning, we will be making a formal submission today.****Thank you,****P. K. Narang, Ph.D., F.C.P.****APPEARS THIS WAY
ON ORIGINAL**

Office of:
P.K. Narang, Ph.D., F.C.P.
Liaison Director, New Drugs
Global Regulatory Affairs

Telephone No. (616) 833-9896
Facsimile No. (616) 833-8237

October 15, 1999

Lisa Rarick, M.D.
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-874
Lunelle™ Monthly Contraceptive Injection
(Medroxyprogesterone acetate and Estradiol cypionate
Injectable Suspension)

GENERAL CORRESPONDENCE
Modified Phase IV Commitment

Dear Dr. Rarick

Per our discussion from this morning, please find below the modified Phase IV commitment.

Hope this meets your recommendation.

[Redacted content]

NDA 20-874
Page 2

*Bone Mineral Density: An evaluation of the effects of LUNELLE™ Monthly
Contraceptive Injection on bone mineral density.*

P&U commits to seek Division's guidance by further discussion and finalization of specific protocol aspects within 6 months from the date of the 'approval' letter. P&U will seek agreement with FDA on key studies/designs prior to initiation of these trials.

If you have any questions regarding this submission, please contact me at (616) 833-9896. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

[/S/]
P.K. Narang, Ph.D., F.C.P.
Director

PKN:SEH
Attachments

cc: Jennifer Mercier (Desk Copy)

APPEARS THIS WAY
ON ORIGINAL

OCT 15 1999

**Division Director Memo
New Drug Application**

NDA: 20-874

Sponsor: Phamacia and Upjohn

Drug: Lunelle™ monthly contraceptive injection (medroxyprogesterone acetate and estradiol cypionate) 0.5mL injectable formulation

Indication: Pregnancy Prevention

Date initial NDA received: September 26, 1997

Date of first action: September 25, 1998

Date of Complete Response: April 16, 1999

Date of memo: October 15, 1999

This product, consisting of 25 mg medroxyprogesterone acetate and 5 mg estradiol cypionate, intended as a once monthly injection for the prevention of pregnancy, is currently marketed in several Latin American and Asian countries. This once-a-month estrogen/progestin combination product theoretically offers the potential advantage of improved compliance, although similar side effect profile, as compared to once-daily combination oral contraceptives. As compared to Depo-provera (depot-medroxyprogesterone acetate or DMPA), a progestin-only three monthly injectable product, the potential advantages of a monthly combination estrogen/progestin injectable product include possible improved bleeding patterns and, theoretically, advantages in terms of effects on bone mineral density, and suppression of ovulation.

In the initial 1997 application three major controlled trials were submitted and reviewed. All three were performed under the sponsorship of the World Health Organization.

As assessed and summarized in the 1998 "Joint Medical Officer" review, several issues resulted in a non-approval action at that time. The primary concerns revolved around issues of inclusion criteria used (many women enrolled may not have been at risk of pregnancy), lack of necessary pregnancy testing, high loss to follow-up, lack of adherence to protocol, as well as significant variation in discontinuations. The trials also allowed for concurrent treatment of vaginal bleeding with hormonal products that could have affected efficacy (including use of other contraceptive methods).

Along with concerns regarding the ability to assess effectiveness in these trials, several concerns regarding the ability to adequately assess safety were raised in the review. Minimal safety information was collected, the information was classified retrospectively, and no case report forms were available for two of the three studies.

At the time of the non-approval action in 1998, the sponsor had initiated a phase III trial in the US. The results of this study are presented in this April, 1999 submission.

As is described by both the Medical Officer and Group Leader memos, the US trial adequately demonstrates efficacy (pregnancy rates over one year are supportive of earlier claims of <1% failure in one year). The trials reviewed also support safety of this product (adverse event profile, aside from bleeding-related events, is consistent with that of other hormonal contraceptive methods).

The theorized advantages of including an estrogen in this contraceptive product were not substantially supported by the data presented in this application.

The first potential advantage—improved compliance as compared to daily oral contraceptives—was addressed in the US trial. In this trial compliance was measured, but the trial suffers from certain design characteristics that make the direct comparison difficult. In the US trial, for example, subjects self-selected the method chosen and thus the study group was not randomized or blinded. This self-selection also raises issues of baseline differences or bias. For example, subjects' previous oral contraceptive experience would likely have influenced their contraceptive method choice on entrance to this study. As can be seen from the 1999 Medical Officer review (page 13), compliance (as measured in the US trial) appears to be better with the daily oral preparation as compared to the monthly injectable.

A second purported advantage of the addition of an estrogen to the injectable product involves the theory that the use of a once-a-month combined hormonal contraceptive would result in bleeding patterns similar to those seen in naturally cycling women and/or women using combined oral contraceptives. In other words, it was hoped to show that monthly injections would result in monthly uterine bleeding similar to that found in naturally cycling women and that induced pharmacologically in women using combined oral contraceptives. A regular bleeding pattern, if confirmed for Lunelle, might then address a major side effect found with DMPA three-monthly injectable—irregular bleeding and amenorrhea.

The US trial was designed specifically to support this assertion. The primary outcome variable in the US trial was uterine bleeding pattern. The trial compared (in an 8:3 ratio) subjects using Lunelle versus those using Ortho-Novum 7/7/7—an approved "triphasic" combined oral contraceptive product.

The US trial results revealed that "normal" bleeding patterns throughout the trial occurred in 9.0% of Lunelle users and 36.8% of the oral contraceptive group. For the last 10th-12th month of a 15-month evaluation, 41.4% of Lunelle users experienced regular bleeding compared to 72.3% in the oral contraceptive group.

One might argue that the bleeding patterns, although not as similar to those found in oral contraceptive users as hoped are improved compared to the approved three-monthly injectable product (DMPA). This argument has not been directly confirmed in trials to date.

Another theoretical advantage of the addition of estrogen to DMPA is in the area of bone mineral density protection. Use of progestin-only injectables may be considered among the risk factors for development of osteoporosis. Formal studies on the effect of bone mineral density in women receiving Lunelle have not been conducted. The pharmacokinetics profile of the estrogen component of Lunelle is comparable to preovulatory estradiol levels. This estrogen profile might contribute to a positive effect on bone.

In terms of possible benefits derived from the addition of estrogen, the sponsor also asserts that the estrogen component of the product is associated with a reduced risk of ovulation although data included in this application do not support this conclusion.

Several significant clinical differences between the combined injectable product versus the current progestin-only three-month injectable exist, although a direct "head-to-head" comparison trial has not been performed. With DMPA three-monthly injectable there is a high incidence (about 50%) of amenorrhea after one year of use. With the once a month combined product the rate of amenorrhea at one year of use was 4.1%. There is also a significant difference in the time needed for return to ovulation and fertility where Lunelle shows a more rapid return to ovulation/fertility as compared to DMPA.

Chemistry and Manufacturing Controls

On October 14, 1999 the Division was alerted to findings of major "Good Manufacturing Practices" (GMP) deficiencies at the Kalamazoo, Michigan manufacturing plant. The GMP deficiencies are listed as "significant" and apply to all small volume parenterals manufactured at this facility. The office of compliance has recommended a "withhold approval" recommendation.

Pediatric Studies

Labeling for Lunelle will include standard pediatric wording similar to other hormonal contraceptives. This section reads: "Safety and efficacy of Lunelle monthly contraceptive injection have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under 16 years of age and users 16 years of age and older. Use of this product before menarche is not indicated."

Specific further studies in children or requests for studies in children are not required at this time.

Recommendations

Until the GMP deficiencies are satisfactorily resolved, the Division recommends an approvable action for Lunelle monthly contraceptive injection for the indication "prevention of pregnancy". Our labeling comments will be conveyed with the action letter.

The Division also proposes that the sponsor be required to address the potential advantages/disadvantages of the addition of the estrogen component more fully. A discussion of potential post-approval studies to address these issues was begun on October 12th. At that time, and in a subsequent facsimile correspondence on October 14, the sponsor agreed to work with the division to develop clinical trials in order to support the benefit of added estrogen. The three areas under consideration for further development include comparison of bleeding patterns, ovulation rates and bone mineral density changes between Lunelle and MPA alone.

LS
10/15/99
Lisa Rarick, MD
Director
DRUDP, HFD-580

cc: NDA 20-874
HFD-580/Allen/Hixon/Mann
HFD-103/Houn/Raczkowski

APPEARS THIS WAY
ON ORIGINAL

Printed by Lana Pauls
Electronic Mail Message

Date: 14-Oct-1999 03:24pm
From: David Morse
CDER/DAVDP) (MORSED
Dept: HFD-530 CRP2 S433
Tel No: 301-827-2330 FAX 301-827-2523

Subject: Label Review for NDA 20-874 (Lunelle) attached

Bronwyn

I've attached my comments for the Lunelle Injection action package and proposed product label. There's not much for P/T to say about this one.

A hard copy of my memo and the action package for Lunelle are on the way back to you via Mark Goldberger.

Dave Morse

APPEARS THIS WAY
ON ORIGINAL

Teleconference Minutes

Date: October 14, 1999 **Time:** 3:45-4:15 PM **Location:** Parklawn; 13B-45

NDA 20-874 **Drug:** Lunelle™ Monthly Contraceptive Injection
(medroxyprogesterone acetate and estradiol cypionate)

Indication: Contraception

Sponsor: Pharmacia & Upjohn Company

Type of Meeting: Guidance

Meeting Chair: Florence Houn, M.D.

External Lead: P.K. Narang, Ph.D.

Meeting Recorder: Jennifer Mercier, B.S.

FDA Attendees:

Florence Houn, M.D. – Director, Office of Drug Evaluation III (ODEIII; HFD-103)

Lisa Rarick, M.D. – Director, Division of Reproductive and Urologic Drug Products
(DRUDP; HFD-580)

Susan Allen, M.D. – Team Leader, DRUDP (HFD-580)

Dena Hixon, M.D. – Medical Officer, DRUDP (HFD-580)

John Gibbs, Ph.D. – Director, Division of New Drug Chemistry II (DNDCII; HFD-820)

David Lin, Ph.D. – Chemist, DNDCII @ DRUDP (HFD-580)

Bronwyn Collier – Associate Director, ODEIII (HFD-103)

Terri Rumble, B.S.N. – Chief, Project Management Staff, DRUDP (HFD-580)

Jennifer Mercier, B.S. – Regulatory Project Manager, DRUDP (HFD_580)

External Attendees:

Dr. Charlie Wajszczuk, Clinical Program Leader

Dr. Roger Garceau, Director, Clinical Development

Dr. P.K. Narang, Director, Global Regulatory Affairs

Dr. Dan Mannix, Senior Director, Global Regulatory Affairs

Meeting Objective: To discuss issues regarding the approvability of this product.

Background: The Division became aware of some GMP problems for the small volume parenterals manufacturer. The problems were significant enough that the Office of Compliance issued a "withhold recommendation" on all products for this manufacturer. This required this Division to inform the sponsor of these issues prior to the user fee date of October 16, 1999.

Discussion:

1. GMP Inspection

- there were serious GMP problems with the small volume parenterals manufacturer

- this is an approvability issue
- this does encompass all similar products
- the recommendation from the chemist will be a non-approval

2. Correction of the formulation

- the inert ingredients are not the same in the label as listed in the NDA
- the sponsor clarified the process and the calculations and why the formulation appears to be different
- the sponsor sent an email to Dr. David Lin regarding the difference and Dr. Lin will review and make his final recommendation
- if the formulation is different than what was used in the clinical trials, this will constitute a deficiency that must be addressed

3. Phase 4 commitment

Decisions made:

- the GMP deficiencies do not allow for an approval
- an approvable letter will be issued if the formulation issue is found acceptable to Dr. Lin
- Phase 4 commitments will be issued when an approval action is taken
- a complete response to this approvable letter will be the satisfactory resolution of the 483 (GMP issues) and labeling negotiations will resume

After Meeting Note:

- the formulation issue is acceptable to Dr. Lin

Unresolved decisions: None

Action Items:

- request fax copy of 483
- fax meeting minutes to sponsor within 30 days

/s/

Minutes Preparer

/s/

Concurrence, Chair

cc:

Original NDA

HFD-580/DivFile

HFD-580/Rumble/Mercier

HFD-580/Rarick/Mann/Hixon/Allen/Rhee/Lin

HFD-820/Gibbs

drafted: October 19, 1999

concurrence: Rumble

10.20.99/Rarick10.22.99/Collier10.21.99/Hixon10.21.99/Gibbs10.21.99/Lin10.29.99/Houn10.20.99

final: October 29, 1999

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

Memorandum

OCT 14 1999

Date: 14 October 1999

From: David E. Morse, Ph.D.
Asc. Director (Pharm./Tox.), Office of Drug Evaluation III

To: Florence Houn, M.D.
Director, Office of Drug Evaluation III

Cc: Lisa Rarick, M.D., Dir., HFD-580
Alex Jordan, Ph.D., TL Pharm./Tox., HFD-580

Subject: NDA 20-874
LUNELLE® Monthly Contraceptive Injection
Medroxyprogesterone acetate and Estradiol cypionate
Review of Pharm./Tox. Sections of Proposed Product Label

I. Materials Included in Review

1. Pharm./Tox. Review of IND 52,624, 3 March 1997, written by Krishan L. Raheja, DVM, Ph.D.
2. Pharm./Tox. TL Memorandum for NDA 20-874, written by Alex Jordan, Ph.D.
3. NDA 20-874 Approval Package, with Draft Product Labeling (dated 6 Oct. 1999).

II. Comments and Conclusions

1. In accordance with current labeling practice for hormonal contraceptive agents, all references to non-clinical toxicology studies conducted with the combination drug product (or the individual components of the combination) have been removed from the Carcinogenesis, Mutagenesis, Impairment of Fertility and Pregnancy sections of the proposed (draft) product label. Within the specified product label sections, reference is made to the Warnings and Contraindications sections of the product label, which contain summary risk evaluations of carcinogenic and reproductive effects evaluated in epidemiology studies of hormonal contraception.

In accordance with current labeling practice for all hormonal contraceptive agents, LUNELLE® Monthly Contraceptive Injection has been designated Pregnancy Category "X".

2. It is recommended that the proposed label section pertaining to the "Return of Ovulation and Fertility" be moved to a position immediately following the label section on Pregnancy, so as not to confuse the sections typically derived from non-clinical and clinical data.
3. Consideration should be given to the inclusion of information on breast milk drug concentration and neo-natal drug exposure in woman taking hormonal contraceptives during lactation.

III. Summary

A review of the action package for NDA 20-874, LUNELLE® Monthly Contraceptive Injection, suggests that the product has been adequately evaluated in multiple non-clinical safety studies for approval of the requested indication. The proposed product label, with possible revision as suggested in the preceding section, adequately reflects the safety data for this product.

The proposed Package Insert for LUNELLE® Monthly Contraceptive Injection, appears to conform with current labeling practices as related to the inclusion/non-inclusion of non-clinical safety assessment data for hormonal contraceptive agents.

APPEARS THIS WAY
ON ORIGINAL

Memorandum

To: NDA 20-874, Lunelle Monthly Contraceptive Injection (medroxyprogesterone acetate
and estradiol cypionate injectable suspension)

Through: Moo-Jhong Rhee, Ph.D.

From: David Lin, Ph.D.

Date: October 14, 1999

Re: Establishment Evaluation Request and Labeling

/S/

10/14/99

10/14/99

OCT 14 1999

The District Office issues a withhold recommendation on October 14, 1999 for the Pharmacia and UpJohn sterile drug product manufacturing facility based on significant GMP deficiencies. This facility now has a potential OAI (official action indicated) status. The Office of Compliance concurred with the withhold recommendation on October 14, 1999 (see attached EER).

The final labeling is pending.

This NDA is not approvable from a CMC point of view.

APPEARS THIS WAY
ON ORIGINAL

cc:

Orig. NDA #20-874
HFD-580/Division File
HFD-580/JMercier
HFD-580/MRhee/DLin

R/D Init by: MJ Rhee

Filename: nda20874.6 (doc)

FDA CDER EES
 ESTABLISHMENT EVALUATION REQUEST
 DETAIL REPORT

Application: NDA 20874/000
 Stamp: 26-SEP-1997
 Regulatory Due: 16-OCT-1999
 Applicant: PHARMACIA AND UPJOHN
 7000 PORTAGE RD
 KALAMAZOO, MI 490010199
 Priority: 4S
 Org Code: 580

Action Goal:
 District Goal: 27-MAY-1998
 Brand Name: _____
 Estab. Name: _____
 Generic Name: ESTRADIOL
 CYPIONATE/MEDROXYPROGESTERONE
 Dosage Form: (SUSPENSION)
 Strength: 5 MG/25 MG

Application Comment:

FDA Contacts: ID = 115760
 R. SEEVERS (HFD-120) 301-594-2850, Project Manager
 M. RHEE (HFD-580) 301-827-4237, Review Chemist
 Team Leader

Overall Recommendation: ACCEPTABLE on 10-NOV-1997 by J. D AMBROGIO (HFD-324) 301-327-0062

Establishment: _____

DMF No: _____ AADA:
 Responsibilities: _____
 Profile: GSP OAI Status: NONE
 Estab. Comment: " _____ (on 29-OCT-1997
 by R. SEEVERS (HFD-120) 301-594-2850)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-OCT-1997				DAMBROGIOJ
OC RECOMMENDATION	29-OCT-1997			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: 1810189
 PHARMACIA AND UPJOHN CO
 7000 PORTAGE ROAD
 KALAMAZOO, MI 49001

DMF No: _____ AADA:
 Responsibilities: DRUG SUBSTANCE MANUFACTURER
 FINISHED DOSAGE MANUFACTURER
 Profile: CSN OAI Status: NONE
 Estab. Comment: THIS SITE MANUFACTURES BOTH DRUG SUBSTANCES. IT ALSO MANUFACTURES
 THE DRUG PRODUCT FROM THE STERILIZED DRUG SUBSTANCES (on 29-OCT-
 1997 by R. SEEVERS (HFD-120) 301-594-2850)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-OCT-1997				SEEVERSR
OC RECOMMENDATION	29-OCT-1997			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Profile: SVS OAI Status: POTENTIAL OAI
 Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-OCT-1997				DAMBROGIOJ
SUBMITTED TO DO	29-OCT-1997 10D				DAMBROGIOJ
DO RECOMMENDATION	07-NOV-1997			ACCEPTABLE BASED ON FILE REVIEW	MROBINSO

DET-DO COMPLETED A COMPREHENSIVE GMP INSPECTION OF PROFILE CLASS SVS

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

(_____) DATED 10/20-30/97. NO FDA-483 WAS
ISSUED AND THE REPORT WILL BE CLASSIFIED NAI.
OC RECOMMENDATION 10-NOV-1997

ACCEPTABLE DAMBROGIOJ
DISTRICT RECOMMENDATION

APPEARS THIS WAY
ON ORIGINAL



Pharmacia & Upjohn

Office of:
P.K. Narang, Ph.D., F.C.P.
Liaison Director, New Drugs
Global Regulatory Affairs

Telephone No. (616) 833-9896
Facsimile No. (616) 833-8237

October 13, 1999

Lisa Rarick, M.D.
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-874
Lunelle™ Monthly Contraceptive Injection
(Medroxyprogesterone acetate and Estradiol cypionate
Injectable Suspension)

GENERAL CORRESPONDENCE
LABELING: Physician and Patient Insert
Phase IV Commitment

Dear Dr. Rarick

Per our teleconference of October 12, 1999, Pharmacia and Upjohn (P&U) is pleased to submit the following labeling pieces for LUNELLE™ Monthly Contraceptive Injection. We would also like to note that all changes recommended yesterday by the Division and Dr. S. Allen have been duly incorporated. Thus, this submission contains a copy of what we trust will be final (agreed to for PI) labeling.

1. Physician Insert Labeling (Revised; P&U: dated 10/12/99)
2. Patient Insert Labeling (Revised, P&U: dated 10/12/99)

An electronic copy of items 1 and 2 was also sent to Ms. Mercier earlier today. Data supporting the inclusion of the statement on weight gain/loss Drs. Allen and Hixon asked for is also provided (see Attachment A). A "™" symbol has been placed after every occurrence of Lunelle in the PI and PPI as advised by Ms. Mercier on October 13, 1999.

Labeling: Non-Insert

P&U submitted the 'Non-insert labeling' yesterday addressing all the recommendations of the reviewer. Ms. Mercier and Dr. David Lin called and informed us today (Oct 13) that the non-insert

NDA 20-874

Page 2

labeling was acceptable, however we must show where the LOT# and EXP date would be placed on the vial label, when printed on-line (see Attachment B).

Phase IV Commitment:

Bone Mineral Density: An evaluation of the effects of LUNELLE™ Monthly Contraceptive Injection on bone mineral density.

P&U commits to seek Division's guidance by further discussion and finalization of specific protocol aspects within 6 months from the date of the 'approval' letter. P&U will seek agreement with FDA on key studies/designs prior to initiation of these trials.

If you have any questions regarding this submission, please contact me at (616) 833-9896. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

P.K. Narang, Ph.D., F.C.P.
Director

PKN:SEH
Attachments

cc: Jennifer Mercier (Desk Copy)

APPEARS THIS WAY
ON ORIGINAL

NDA ACTION LETTER ROUTING RECORD

NDA# 20-874 DATE REC. 10/13/99
 DRUG Lunelle HFD 580
 TYPE OF LETTER: (AP) (AE) (NA) DRUG CLASSIFICATION: _____
 PATENT INFO REC.: ✓ SAFETY UPDATE: ✓
 PHASE IV COMMITMENT: ✓

REVIEWER	RECEIPT	ACTION
Bronwyn Collier Special Assistant to the Director	Date <u>10/13/99</u> Initials <u>BEC</u>	Date <u>10/13/99</u> Initials <u>BEC</u>

COMMENTS: see attached review.

Chemistry Review Date 10/13/99 Initials SAK Date 10/14/99 Initials SAK

COMMENTS: EEA out of date, one firm pending OAI needs to be resolved or Approvable letter rather than approval letter issued.
Memo OK 3/5/98. DAFS for DS were found adequate to support application.
No specification in DP to ensure suspension covered by USP content uniformity.
Trademark review OK. 6/7/99, Labeling formulation does not correspond to that in the CMC review. Question should be resolved prior to approval.
Container label should also say prominence of established name should be acceptable not just 1/2 size.

Pharmacology & Toxicology Review Date _____ Initials _____ Date _____ Initials _____

P. BOTSTEIN, M.D. Date _____ Initials _____ Date _____ Initials _____
 Acting Director, ODE III Returned to Dfvision for Corrections _____ Forward _____

COMMENTS:

APPEARS THIS WAY
ON ORIGINAL

**ADMINISTRATIVE REVIEW OF NDA (review pkg) ~
OFFICE OF DRUG EVALUATION III**

NDA: 20-874

Drug: Lunelle Monthly Contraceptive Injection
(medroxyprogesterone acetate and estradiol cypionate injectable suspension)

Classification: 4 S

Sponsor:

Project Manager/CSO: Jennifer Mercier

Reviewer: Bronwyn Collier 151 10/15/99

Review Date: October 13, 1999

Review Cycle 1

Date Submitted: September 25, 1997

Date Received: September 26, 1997

Primary Goal Date: September 26, 1998

Extended Primary Goal Date: not applicable

Secondary Goal Date: not applicable (98 cohort)

Extended Secondary Goal Date: not applicable

Action: not approvable (September 25, 1998)

Review Cycle 2

Date Submitted: (AZ) April 15, 1999

Date Received: April 16, 1999

Primary Goal Date: October 16, 1999 (Class 2 resubmission)

Proposed Action: approval

	CONFORMS TO REGS & CDER POLICY		COMMENTS
	YES	NO	
ACTION LETTER			Needs revision to correct submission dates.
PATENT STATEMENT	X		
EXCLUSIVITY CHECKLIST	X		
DEBARMENT STATEMENT	X		
PEDIATRIC PAGE	X		
NOMENCLATURE	X		Found acceptable by LNC.
DSI AUDITS			Dunston and Merritt found NAI. — audit listed as pending in COMIS
FACILITY		X	Inspection report out of

INSPECTIONS		date (acceptable 11/10/97). Pharmacia-Upjohn facility is a potential OAI. DMPQ contacted to determine current recommendation.
REVIEWS	RECOMMENDATION	COMMENTS
DIV. DIR. MEMO	AP with phase 4 commitments.	Provided in draft.
TL MEMO	AP with phase 4 commitments	
CLINICAL	AP with phase 4 commitments.	
SAFETY UPDATE		Included in MO review dated 9/23/99.
STATISTICAL		Completed in review cycle 1.
BIOPHARM	AP	Recommendations for labeling revision.
CMC	AP	
EA		Completed 1 st review cycle.
MICRO (validation of sterilization)		Completed 1 st review cycle.
STABILITY (stats)		Included in chem reviews for 1 st review cycle.
PHARM/TOX	AP	
CAC (stats)		Not applicable.
CAC/ECAC REPORT		Not applicable.

Labeling: Revised labeling to be enclosed with approval letter. Documentation of agreement by the applicant re the final wording of the package insert is needed.

Phase 4 Commitments: _____

Documentation of the phase 4 commitments is needed.

Advisory Committee Meeting: not applicable.

Recommendations:

1. Letter: Revisions to correct submission dates needed. The division should consider whether a waiver of pediatric studies for the indication to be approved is appropriate. If so, the waiver paragraph can be included in the letter rather than a request for a pediatric plan.
2. Status of the — clinical audit needs to be determined. If the division deems the study acceptable based on assurances

from audits of the [redacted] and [redacted] sites, this should be documented and the [redacted] inspections canceled.

3. Documentation of the phase 4 commitments is needed.
4. Facilities inspection out of date. Possible OAI status. DMPQ to determine current recommendation.

UPDATE (10/15/99)

1. Action to be approvable based on recommendation from compliance re the GMP deficiencies at the manufacturing facility. Pediatric study waiver will be considered for future approval action.
2. [redacted] clinical audit NAI.
3. Phase 4 commitments documented.
4. [redacted]

BC/10/13/99

APPEARS THIS WAY
ON ORIGINAL



Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

Office of:
P.K. Narang, Ph.D., F.C.P.
Liaison Director, New Drugs
Global Regulatory Affairs

Telephone No. (616) 833-9896
Facsimile No. (616) 833-8237

October 12, 1999

Lisa Rarick, M.D.
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-874
Lunelle™ Monthly Contraceptive Injection
(Medroxyprogesterone acetate and Estradiol cypionate
Injectable Suspension)

General Correspondence
Labeling: Non-Insert

Dear Dr. Rarick

On October 6, 1999, Pharmacia and Upjohn (P&U) received from the Division a proposal (via FAX) with recommendations for the LUNELLE Monthly Contraceptive Injection Physician Insert Labeling. Noted at the end were several recommendations regarding needed changes to 'non-insert labeling' submitted in our September 27, 1999 submission.

Attached please find the revised 'non-insert' labeling as discussed with and promised to the Chemistry Reviewer during our Oct 7, 1999 teleconference. We have made all changes as recommended, except putting the established name within parenthesis. However, additional space has been added that clearly separates it from the proprietary name. Our internal policy is to not place 'parenthesis' around established name; most of our current products do not have one (Dr. Dan Borin (FDA) had discussed this with P&U staff and accepted); the special pathogens division accepted this for Dalacin Vaginal Ovules as recently as August 99.

Attached is labeling (1 each) for the following:

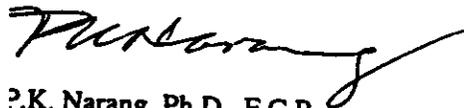
1. Vial
2. Sample Vial
3. 1 Sample Carton
4. 3, 25, and 1 pack cartons

An electronic copy (.pdf file format) of the above labels was also forwarded to Ms. Mercier on 10/12/99. We would greatly appreciate a quick review and blessing for this 'non-insert' labeling.

If you have any questions regarding this submission, please contact me at (616) 833-9896. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY



P.K. Narang, Ph.D., F.C.P.
Director

Attachments

APPEARS THIS WAY
ON ORIGINAL

cc: Jennifer Mercier (Desk Copy)

BEST POSSIBLE COPY

**Pharmacia & Upjohn**7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000Office of:
P.K. Narang, Ph.D., F.C.P.
Liaison Director, New Drugs
Global Regulatory Affairs
Telephone No. (616) 833-9896
Facsimile No. (616) 833-8237

October 8, 1999

Lisa Rarick, M.D.
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857**RE: NDA 20-874
Lunelle™ Monthly Contraceptive Injection
(Medroxyprogesterone acetate and Estradiol cypionate
Injectable Suspension)****GENERAL CORRESPONDENCE
INTERNATIONAL LABELING**

Dear Dr. Rarick:

On October 7, 1999, Pharmacia and Upjohn (P&U) received a request from the Division for international labeling of LUNELLE Monthly Contraceptive Injection. This drug product is neither registered nor marketed by P&U in any international markets.

Medroxyprogesterone acetate (25mg) and Estradiol cypionate (5 mg) Injectable Suspension (CYCLOFEM and CYCLOFEMINA) is marketed in several countries by other companies (i.e. Brazil, Chile, Mexico, Indonesia, etc). Though P&U attempted, it has not yet been able to find labeling for their products as of this day.

If you have any questions regarding this submission, please contact me at (616) 833-9896. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

P.K. Narang, Ph.D., F.C.P.
DirectorPKN:crdt
cc: Jennifer Mercier (Desk Copy)

ORIGINAL
ORIG AMENDMENT;
BL



Pharmacia & Upjohn

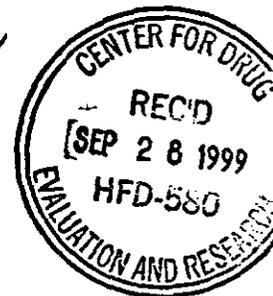
7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

Office of:
P.K. Narang, Ph.D., F.C.P.
Liaison Director, New Drugs
Global Regulatory Affairs

Telephone No. (616) 833-9896
Facsimile No. (616) 833-8237

September 27, 1999

Lisa Rarick, M.D.
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 20-874
Lunelle™ Monthly Contraceptive Injection
(Medroxyprogesterone acetate and Estradiol cypionate
Injectable Suspension)

GENERAL CORRESPONDENCE
LABELING: Physician Insert and Non-Insert

Dear Dr. Rarick

On September 20, 1999 Pharmacia and Upjohn (P&U) received from the Division an initial proposal (via FAX) with recommendations for the Physician Insert Labeling submitted in our April 15, 1999 amendment to the above NDA for LUNELLE Monthly Contraceptive Injection. Ms. Mercier also requested that we forward to you the 'non-insert' labeling as well. We are pleased to provide you with the following:

1. Physician Insert Labeling (Revised; P&U : version dated 9/24/99)
 - 92499.doc (strikeout version)
 - 924pi-c.doc (clean version)
2. Non-Insert Labeling (Actual sizes)
 - Immediate container
 - Outer carton for single pack (Item A), complimentary pack (Item B), three pack (Item C), and 25 pack (hospital use; Item D)

Though a copy of Item 1 above was electronically sent earlier today via e:mail to you to expedite the reviewing at your end, a copy has also been placed on the enclosed diskette as well in WORD 6.0.

BEST POSSIBLE COPY

P&U wishes to draw your attention to Item 11 (Bleeding Irregularities) under WARNINGS and Item 6 (Weight Change) under PRECAUTIONS which have undergone revisions of note. It is our belief that inclusion of 'clinical undesirability rates' and 'bleeding patterns' per Belsey's definitions may be less meaningful for the 'end user', the physician, and not very consistent with labeling for existing combined oral combination products. The 'weight change' modification keeps the 'needs of an individual woman' in mind during consultation with her physician regarding the product. Existing data on weight change (previously provided in our amendment) were recomputed and are included under Attachment 4.

Per your request and considering the modified Physician's Insert, we intend to submit the 'Patient Insert' to you within the next 2-3 days.

If you have any questions regarding this submission, please contact me at (616) 833-9896. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

P.K. Narang

P.K. Narang, Ph.D., F.C.P.

Director

Regulatory Affairs

PKN:lmf

Attachments

cc: Jennifer Mercier (Desk Copy)

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

APPEARS THIS WAY
ON ORIGINAL

- SEP 27 1999

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 24, 1999

FROM: Lisa A. Kammerman, Ph.D., Team Leader (HFD-715) /S/ 9/24/99

TO: NDA 20-874 (Lunelle Monthly Contraceptive Injection)

SUBJECT: Statistical review of amendment dated 4/15/99

This amendment to NDA 20-874 is a response to a non-approvable letter from HFD-580. The amendment contains one clinical study. Because the clinical review of the study focused on a single treatment arm that did not have any pregnancies, a statistical review was not needed.

Concur: E. Nevius, Ph.D. (HFD-715) /S/ 9-27-99

cc:

Archival NDA 20-874

HFD-580

HFD-580/Allen/Hixon/Mercier

HFD-715/Nevius/Kammerman

APPEARS THIS WAY
ON ORIGINAL

Memorandum

To: The file for NDA 20-874 (lunelle Monthly Contraceptive Injection)

SEP 27 1999

From: Alex Jordan, PhD
Team Leader, Pharmacology, DRUDP

Date: September 27, 1999

Subject: Labeling issues raised by Dr. Joe DeGeorge in an email dated 9/24/98.

- 1) No doses or comparisons of exposure were provided
- 2) Presentation of the 2-year monkey study as an assessment of carcinogenic potential is misleading and should not be described as a satisfactory assessment of carcinogenicity.
- 3) Information on drug excretion in breast milk and the possible effects of the drug on the neonate is not provided.

The Carcinogenesis, Mutagenesis, and Impairment of Fertility section of the label were revised and references to were deleted in accordance with the labeling of other oral contraceptives. Information on drug excretion in breast milk has been included.

APPEARS THIS WAY
ON ORIGINAL



Food and Drug Administration
Rockville, MD 20855

SEP 21 1999

[]
Dear _____

The purpose of this letter is to inform you of our conclusions concerning your conduct of the clinical study (protocol # M/5415/0004) of _____ that you conducted for Pharmacia & Upjohn.

Between August 9 and August 11, 1999, Ms. Stephanie E. Hubbard and Ms. Brandy E. Davis, representing the Food and Drug Administration (Agency), inspected the study identified above. We reviewed the inspection report prepared by Ms. Hubbard, and copies of study records obtained during the inspection. Based on our review, we conclude that you conducted your study in compliance with the Federal regulations that apply to clinical studies of investigational new drugs and with acceptable standards of good clinical practice.

This inspection is part of the Agency's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

We appreciate the cooperation shown Ms. Hubbard and Ms. Davis during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

[S/S]
Dette L. Barton, Ph.D., M.D.
Chief, Good Clinical Practices Branch 1 (HFD-46)
Center for Drug Evaluation and Research
7520 Standish Place, Suite 125
Rockville, MD 20855

APPEARS THIS WAY
ON ORIGINAL

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bcc:

- HFA-224
- HFD-580 Doc. Rm. NDA 20-874/TND
- HFD-580 Review Div. Dir.
- HFD-580 MO Hixon
- HFD-580 CSO/PM Mercier
- HFD-45 Reading File
- HFD-46 Chron File
- HFD-46 CIB File _____
- HFD-46 Turner
- HFD-46 Prager
- HFR-SE-150 DIB Kline
- HFR-SE-150 BIMO MONITOR Todd
- HFR-SE-150 INSPECTOR Hubbard

CFN: _____

Field Classification: NAI

Headquarters Final Classification:

- 1) NAI
- 2) VAI no response required
- 3) VAI-R response requested
- 4) VAI-RR adequate response received before VAI-R ltr issued
- 5) OAI-W warning letter
- 6) OAI NIDPOE letter

APPEARS THIS WAY
ON ORIGINAL

If the Field and Headquarters classifications are different, explain why:

Deficiencies Noted:

- none
- inadequate consent form
- inadequate drug accountability
- deviations from protocol
- inadequate records
- failure to report ADRs
- other (specify)

O:AGDT _____ gdt
review:BLB:15SEP99

Food and Drug Administration
Rockville MD 20857

SEP 21 1999

[Redacted]

Dear _____

The purpose of this letter is to inform you of our conclusions concerning your conduct of the clinical study (protocol # M/5415/0004) of _____ that you conducted for Pharmacia & Upjohn Company.

Between June 28 and July 21, 1999, Mr. Philip J. Boston and Ms. Pamela J. Walker, representing the Food and Drug Administration (Agency), inspected the study identified above. We reviewed the inspection report prepared by the Agency's inspectors and copies of study records obtained during the inspection. Based on our review, we conclude that you conducted your study in compliance with the Federal regulations that apply to clinical studies of investigational new drugs and with an acceptable standard of good clinical practice.

This inspection is part of the Agency's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

We appreciate the cooperation shown during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

[Signature]

Bette L. Barton, Ph.D., M.D.
Chief, Good Clinical Practices Branch 1 (HFD-46)
Center for Drug Evaluation and Research
7520 Standish Place, Suite 125
Rockville, MD 20855

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

bcc:

HFA-224

HFD-580 Doc. Rm. NDA 20-874

HFD-580 Review Div. Dir. Rarick

HFD-580 MO Hixon

HFD-580 CSO/PM Mercier

HFD-45 Reading File

HFD-46 Chron File

HFD-46 CIB File

HFD-46 Turner

HFD-46 Prager

HFR-SW-450 DIB Bringman

HFR-SW-450 BIMO Monitor Bringman

HFR-SW-450 Inspectors Boston & Walker

CFN: _____

Field Classification: NAI

Headquarters Final Classification:

1)NAI

2)VAI no response required

3)VAI-R response requested

4)VAI-RR adequate response received before VAI-R ltr issued

5)OAI-W warning letter

6)OAI NIDPOE letter

If the Field and Headquarters classifications are different, explain why:

Deficiencies Noted:

none

inadequate consent form

inadequate drug accountability

deviations from protocol

inadequate records

failure to report ADRs

other (specify)

O:\GDTV _____ gdt

MO Notes: The study related records were reviewed for 20 of the 40 subjects enrolled at this site in protocol #M/5415/0004. Based on our review of the EIR, DSI recommends that this study may be used in support of the NDA. No discrepancies were found between the data reported on the CRFs and data on the essential documents.

Group Leader Memorandum

SEP 20 1999

NDA#: 20-874

Drug: Lunelle™ Monthly Contraceptive Injection

Generic Drug Name: Medroxyprogesterone acetate and estradiol cypionate injectable suspension

Indication: Prevention of pregnancy

Dose: 25 mg medroxyprogesterone acetate and 5 mg estradiol cypionate intramuscular injection for monthly administration

Formulation: Injectable suspension

Applicant: Pharmacia & Upjohn Company

Date of submission: April 16, 1999

Date of memorandum: September 20, 1999

Background

Currently, Depo-Provera® [medroxyprogesterone acetate injectable suspension] (DMPA) is the only injectable contraceptive product approved for use in the United States. This product is a progestin-only contraceptive method that is administered every three months to ensure contraceptive effectiveness. The most common reason for discontinuation of either oral or injectable progestin-only contraceptive methods is disruption of menstrual bleeding patterns, resulting in unsatisfactory acceptability profiles for these products.

Lunelle™ Monthly Contraceptive Injection (Lunelle™) is an injectable drug product containing a synthetic progestin and a synthetic estrogen. The estrogen component was added to the progestin component in an attempt to increase the incidence of regular menstrual bleeding patterns and enhance the product's acceptability. Lunelle™ contains 25 mg of medroxyprogesterone acetate (MPA) combined with 5 mg of estradiol cypionate and is administered every 28-30 (not to exceed 33) days for female contraception.

Lunelle™ is marketed as a contraceptive in several countries outside the United States where it is known as CYCLO-PROVERA™. An NDA for this product was submitted to the Division of Reproductive and Urologic Drug Products (DRUDP) of the FDA on September 25, 1997. The

application contained the results from three phase 3 clinical trials sponsored by the World Health Organization (WHO) and thirty-eight additional clinical trials that provided supportive safety and/or efficacy data for the product. Numerous deficiencies were found in the database contained in the original application, resulting in issuance of a not-approvable letter to the sponsor on September 25, 1998. The sponsor subsequently submitted an amendment to the NDA on April 16, 1999 in response to the deficiencies noted in the not-approvable letter.

Prior to submission of the original NDA in 1997, the sponsor had initiated a large U.S. trial (study M/5415/0004) to acquire additional acceptability, efficacy and safety experience with the product when used by U.S. women. This trial was designed primarily as an acceptability trial, but data on efficacy and safety were also collected. Following recommendations from DRUDP, the sponsor amended the protocol for the ongoing study in July of 1998, thereby making it possible for this trial to potentially support marketing approval in the U.S. Thus, the current amendment consists of responses to previously noted deficiencies in the NDA and contains the results from study M/5415/0004 entitled, "CYCLO-PROVERA™ Contraceptive Injection: A Comparative Study of Safety, Patient Acceptability and Efficacy to ORTHO-NOVUM 7/7/7-28 Tablets."

Review of the Clinical Study

Study M/5415/0004 was a non-randomized, open-label, comparative trial of CYCLO-PROVERA™ and Ortho-Novum 7/7/7-28 tablets in 1,100 volunteers. Study participants were permitted to self-select either treatment (e.g., monthly injections of CYCLO-PROVERA™ or daily tablets of Ortho-Novum 7/7/7) in an 8:3 ratio. Volunteers were to receive study drug for up to a 60-week (15-cycle) treatment period. The primary efficacy variable was uterine bleeding pattern, with contraceptive efficacy, general safety and patient acceptability being secondary efficacy variables. Several significant review issues were noted for this application, including (1) limitations in the original U.S. study protocol that prevented an assessment of efficacy in the entire intent-to-treat population, (2) effect of the product on menstrual bleeding patterns in users, and (3) inadequate justification of the estradiol cypionate component of the product.

As noted above, FDA recommendations to the sponsor in July of 1998 resulted in modification of the study protocol so that mandatory pregnancy testing was performed for all volunteers at monthly study visits and at study discontinuation or completion. During review of the original NDA application, it was noted that because of inclusion and exclusion criteria in the protocol for the U.S. trial, many volunteers participating in the study were not at risk or were at reduced risk for pregnancy at enrollment. Subsequently, the sponsor was informed in the September 25, 1998 not-approvable letter that the ongoing U.S. trial should be continued until a minimum of 200 women meeting specific criteria outlined in the not-approvable letter had completed at least 13 cycles of product use. As described in the primary Medical Officer's review, this requirement was met by the sponsor.

Seven-hundred-eighty-two women were enrolled in the CYCLO-PROVERA™ treatment arm, and 321 women were enrolled in the active control arm of the study. Because this was a non-randomized trial that would not permit comparative claims, the primary Medical Officer's review focused on the CYCLO-PROVERA™ treatment arm of the study. Per that review, 300 of the 782 women enrolled in the CYCLO-PROVERA™ treatment arm of the study met the enrollment criteria previously specified by the FDA in the not-approvable letter and completed 15 cycles of product use.

Although the sponsor reported that no pregnancies occurred in the subgroup of women described above, 72 women in the CYCLO-PROVERA™ treatment arm of the study discontinued their participation in the trial prior to completing 15 cycles of use and were not able to be retrospectively contacted to determine pregnancy status at discontinuation. Thus, efficacy could not be ascertained for approximately 10% of the intent-to-treat population in the Lunelle™ treatment arm. Efficacy of the product was demonstrated for the subgroup of 300 women meeting appropriate FDA-specified criteria.

A second significant review issue for this amendment was related to the effect of Lunelle™ on menstrual bleeding patterns throughout the trial. Based upon historical data, continued use of DMPA results in increasing rates of amenorrhea and "infrequent" bleeding, as well as decreasing rates of "irregular" and "prolonged" bleeding. After one year of DMPA use, approximately 50% of women experience amenorrhea. Results from studies with Lunelle™ demonstrated that (1) the rate of amenorrhea following one year of use was significantly lower (4.1%) than that associated with DMPA use, and (2) similarly to DMPA, the rate of "prolonged" bleeding decreased over time, while (3) the rate of "irregular" bleeding remained constant at approximately 30%. Although comparisons across trials have definite limitations, there was insufficient evidence that Lunelle™ produced a more regular bleeding pattern than DMPA if bleeding patterns other than amenorrhea were studied.

The effect of bleeding pattern disturbances on the acceptability profile for Lunelle™ was also examined in the current application. Per the original protocol for the U.S. study and the protocols for the WHO studies previously reviewed, menstrual bleeding patterns were classified as "clinically undesirable" or "normal" for each 90-day reference period of product use. As noted in the primary Medical Officer's review, 58.6% of patients using Lunelle™ had clinically undesirable bleeding patterns during the fourth reference period (corresponding to months 9 to 12 of use), while 41.4% had "normal" bleeding patterns during this use period. Bleeding patterns did not predict discontinuation from the trial nor did they pose a safety risk in that the incidence of anemia throughout the trial was reported as 1.3%. Thus, undesirable bleeding patterns were associated with patient inconvenience, not safety risk.

A third key review issue for this application was related to inadequate justification for the estrogen component of this combination drug product. According to the sponsor, the rationale for the addition of estradiol cypionate to the progestin component of this product was to improve bleeding patterns over those typically seen with other progestin-only contraceptives, particularly

DMPA. As described above, this benefit was not demonstrated from the data provided by the sponsor. In addition, although the sponsor claimed that the estrogen component of the product was associated with a reduced risk of breakthrough ovulation, data contained in the application did not support this position.

Despite the lack of evidence for improvement in bleeding patterns as compared to DMPA, Lunelle™ appears to offer the following advantages over injectable progestin-only contraceptives: (1) a reduced incidence of amenorrhea with continued use; (2) more rapid reversibility of drug effect following discontinuation; (3) more rapid return to fertility following product discontinuation; (4) a theoretical reduction in the amount of bone mineral density (BMD) loss compared to that observed with DMPA use.

Safety data contained in the original application and in the 1998 response-to-deficiencies amendment did not demonstrate an increased risk for estrogen-related adverse events and supported the safety of Lunelle™ as a monthly contraceptive.

The labeling for Lunelle™ was extensively revised from the original version submitted by the sponsor with the application. The final format and content of the information contained in the label was designed to reflect data known and risks associated with combined hormonal contraceptives and with progestin-only injectable contraceptive products.

Conclusions and Recommendations

Although the number and magnitude of the deficiencies in the database for the WHO-sponsored trials which comprised the original NDA did not permit a confident assessment of the safety or efficacy of Lunelle™, data contained in the current amendment does support the safety and effectiveness of Lunelle™ for marketing approval in the U.S. As noted both in this memorandum and in the primary Medical Officer's review, the sponsor did not provide thorough justification for the estrogen component of this combination drug product. In light of this fact, the sponsor will conduct phase 4 commitment studies to further assess the theoretical benefits of the estrogen component as presented in the sponsor's application. These phase 4 studies will assess (1) the effect of Lunelle™ use on BMD and will compare this effect to that seen with DMPA, and (2)

I agree with the primary Medical Officer's assessments and recommend approval of Lunelle™ for the indication of female contraception.


Susan S. Allen, MD, MPH
Team Leader, HFD-580

9/20/99 Cc: NDA 20-874
HFD-580, Division File
SAllen, DHixon, MMann, LRarick

/S/

Meeting Minutes

Date: September 13, 1999 **Time:** 2:30-4:00 PM **Location:** 17B-43

NDA 20-874 **Drug:** Lunelle (medroxyprogesterone acetate and estradiol cypionate injectable suspension)

Indication: Contraception

Sponsor: Pharmacia & Upjohn

Type of Meeting: Labeling

Meeting Chair: Marianne Mann, M.D.

Meeting Recorder: Jennifer Mercier, B.S.

FDA Attendees:

- Florence Houn, M.D. – Director, Office of Evaluation III (HFD-103)
- Marianne Mann, M.D. – Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP @ HFD-580)
- Susan Allen, M.D. – Team Leader, DRUDP (HFD-580)
- Dena Hixon, M.D. – Medical Officer, DRUDP (HFD-580)
- DJ Chatterjee, Ph.D. – Biopharmaceutics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCBP) @ DRUDP (HFD-580)
- Venkat Jarugula, Ph.D. – Biopharmaceutics Reviewer, OCBP @ DRUDP (HFD-580)
- David Lin, Ph.D. – Chemist, Division of New Drug Chemistry II (DNDCII) @ DRUDP (HFD-580)
- Jennifer Mercier, B.S. – Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss the proposed label with revisions as noted.

Decisions made: See attached label. (Recommendations are in bold print.) Multiple revisions were made to this label by the Medical Officer and Team Leader.

Action Items:

- Fax revised label to the sponsor

/S/

Minutes/Preparer

/S/

Concurrente, Chair

UD.

NDA 20-874
Meeting Minutes
Page 2

cc:
Original NDA
HFD-580/DivFile
HFD-580/Rumble/Mercier
HFD-580/Rarick/Mann/Allen/Hixon/Lin/Chatterjee/Jordan/Rhee/Parekh/Kammerman

drafted: September 20, 1999/Mercier
concurrence: Rumble9.21.99/Lin9.28.99/Allen9.24.99/Houn9.21.99/Mann9.24.99/Hixon9.29.99
final: October 6, 1999

MEETING MINUTES

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42 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

⋮

Items^a which this response addresses:

1. A Table with requested cohort sizes
2. Pregnancy test results for a specific, noted cohort
3. Concomitant Steroidal / Hormonal Medication information for another cohort (Attachment 1: Listing)
4. Those noted under 'Information Related to Efficacy'
5. Criteria definitions for 'at risk for pregnancy' and 'not applicable' for condom use (under 'Other Information Needed')

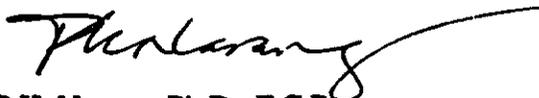
^a [Items 1-3 (page 1) and Items 4, 5 (page 2) of FAX]

We note that the 're-analysis of the Lipid and Blood Pressure' data, requested under 'Other Information needed' was submitted on August 25, 1999. We anticipate providing the responses to the outstanding questions, hopefully, by early next week.

If you have any questions regarding this submission, please contact me at (616) 833-9896. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY



P.K. Narang, Ph.D., F.C.P.
Director, Regulatory Affairs

PKN:kmv

Attachments

(5)
151 9/8/99

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ORIGINAL

NEW CORRESP
NL



Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

Office of:
P.K. Narang, Ph.D., F.C.P.
Liaison Director, New Drugs
Regulatory Affairs

Telephone No. (616) 833-9896
Facsimile No. (616) 833-8237

September 7, 1999

Ms. Jennifer Mercier
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 20-874
Lunelle™ Monthly Contraceptive Injection
(Medroxyprogesterone acetate and Estradiol
cypionate Injectable Suspension)

General Correspondence
Responses to the August 20 and September 1, 1999
Teleconferences

Dear Ms. Jennifer Mercier:

As requested by the Division, Pharmacia and Upjohn (PNU) is pleased to submitted the following items:

1. Responses to the outstanding questions raised during the August 20, 1999 teleconference (Attachment 1).
2. Response to the request for clarification of select items and new cohort estimates per September 1, 1999 teleconference (Attachment 2).

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We appreciate the help and guidance provided to P&U by both Drs. Allen and Hixon during the recent teleconferences. As can be seen from the new table for cohort sizes (under Attachment 2), P&U has 290 women completing at least 13 cycles on Lunelle™ who are considered "at risk" per definitions discussed.

If you have any questions regarding this submission, please contact me at (616) 833-9896. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY



P.K. Narang, Ph.D., F.C.P.
Director, Regulatory Affairs

PKN:lmf

Attachments

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	
CSO INTL:	
	DATE

Handwritten: 9/20/99

*Considered in
NDA review
DRH 9/13/99*

APPEARS THIS WAY
ON ORIGINAL

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DUPLICATE



Pharmacia & Upjohn

SM
7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

Office of:
P.K. Narang, Ph.D., F.C.P.
Liaison Director, New Drugs
Regulatory Affairs

Telephone No. (616) 833-9896
Facsimile No. (616) 833-8237

September 3, 1999

Ms. Jennifer Mercier
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-874
Lunelle™ Monthly Contraceptive Injection
(Medroxyprogesterone acetate and Estradiol
cypionate Injectable Suspension)

General Correspondence
(Impurity - Specification for Drug Product)

Dear Ms. Mercier

Dr. D. Lin (teleconference September 1, 1999), requested Pharmacia and Upjohn (P&U) to provide batch data for MPA used in any clinical lots. Attached please find the requested information.

This is the only clinical lot for which we have batch data. As was stated in the NDA, the extended period over which development of this product took place, information regarding the manufacture and testing of the early clinical supplies is not available. The clinical studies were performed under the auspices of World Health Organization (WHO). Our old records were destroyed in compliance with the internal retention schedules.

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Depo-Provera® and Lunelle™ _____ are manufactured using the same MPA bulk drug material and are referenced to the same DMF (# ____). P&U has shown that this bulk drug material routinely has levels of _____ (data table previously supplied; August 30, 1999 submission). Depo-Provera containing _____ is already commercially available.

Since, Depo-Provera® contains _____ the concentration of MPA compared to that in Lunelle™ (_____) and only half the dose volume is the recommended dose, there is a strong justification for the absence of any safety concerns.

P&U would appreciate receiving a response, if possible, early next week. If you have any questions regarding this submission, please contact me at (616) 833-9896. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY



P.K. Narang, Ph.D., F.C.P.
Director, Regulatory Affairs

PKN:mlw

Attachments

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ORIGINAL

ORIG AMENDMENT

BM.

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000



Pharmacia & Upjohn

Office of:
P.K. Narang, Ph.D., F.C.P.
Liaison Director, New Drugs
Regulatory Affairs

Telephone No. (616) 833-9896
Facsimile No. (616) 833-8237

August 31, 1999

*noted
JTC
9/7/99*



*Noted
JE for AS
9/8/99*

*Discussed in
telecon c sponsor
on 9/1/99
DRH.*

Ms. Jennifer Mercier
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-874
Lunelle™ Monthly Contraceptive Injection
(Medroxyprogesterone acetate and Estradiol
cypionate Injectable Suspension)

General Correspondence
Partial Response to FDA Request dated 8/20/99

Dear Ms. Mercier

On August 20, 1999, during a teleconference, Pharmacia and Upjohn (P&U) was asked by the Division to provide additional information pertaining to specific cohorts of interest for the US clinical trial (10004) submitted in the amendment of April 15, 1999 for registration of Lunelle™. To assist, Drs. S. Allen and D. Hixon faxed a copy of a Table (for various cohorts) they wished for us to complete, along with additional questions for which additional details were deemed necessary.

Appended please find a 'partial response' to the above noted request. Though, during the teleconference, we had advised the Division of possible difficulties in getting to the Depo-Provera information needed to contrast with Lunelle™, it was our intent to have it all done by Aug 27th. Apparently, a bit more time is needed.

If you have any questions regarding this submission, please contact me at (616) 833-9896.
Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

P.K. Narang
P.K. Narang, Ph.D., F.C.P.
Director, Regulatory Affairs

PKN:crdt

cc: Jennifer Mercier (Desk Copy)

*OK
PKN
9-9-99*

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> MEMO
CSO INITIALS: <i>JM</i>
DATE: <i>9/13/99</i>

APPEARS THIS WAY
ON ORIGINAL

66-1-99

/S/

Meeting Minutes

Date: August 31, 1999 **Time:** 9:30-10:30 AM **Location:** 17B-43

NDA 20-874 **Drug:** Lunelle™ Monthly Contraceptive Injection
(medroxyprogesterone acetate and Estradiol cypionate
Injectable Suspension)

Indication: Contraception

Sponsor: Pharmacia & Upjohn

Type of Meeting: 4 Month Status (Internal)

Meeting Chair: Marianne Mann, M.D.

Meeting Recorder: Jennifer Mercier, B.S.

FDA Attendees:

Marianne Mann, M.D. – Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Susan Allen, M.D. – Team Leader, DRUDP (HFD-580)

Dena Hixon, M.D. – Medical Officer, DRUDP (HFD-580)

Ameeta Parekh, Ph.D. – Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Dhruba Chatterjee, Ph.D. – Biopharmaceutics Reviewer, OCPB @ DRUDP (HFD-580)

David Lin, Ph.D. – Chemist, Division of New Drug Chemistry II (DNDCII) @ DRUDP (HFD-580)

Terri Rumble, B.S.N. – Chief, Project Management Staff, DRUDP (HFD-580)

Jennifer Mercier, B.S. – Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss the review status of this application.

Background: Lunelle™ Monthly Contraceptive Injection is a resubmission in response to a previous submission that was Not Approved. Previously, the submission received a not approval based on the lack of meaningful clinical data to support the desired indication.

Decisions made:

Chemistry

- the name Lunelle™ Monthly Contraceptive Injection is acceptable
- the review is complete from the previous submission, approval will be recommended, pending final labeling review

Biopharmaceutics

- concern regarding the return to ovulation after use of this product
- review will be complete by due date

Clinical

- communicated to sponsor concern regarding addition of estrogen component to this product: does the estrogen component add to efficacy or improve safety?
- requested from sponsor bleeding profile for Depo-Provera
- sponsor to reanalyze the risk/benefit for this product
- may need to require a Phase 4 commitment for approval of this product; a head-to-head trial with Lunelle versus Depo-Provera to address benefits of Lunelle

Efficacy

- the recommendation of 200 patients completing 13 cycles may not be met given the number of patients who were studied with various confounding factors that put them at decreased risk for pregnancy

Label

- _____
- weight gain will have to be assessed and put into the label
- unacceptable bleeding patterns will have to be addressed

Pharmacology

- review is complete from previous submission; recommended approval
- labeling will be reviewed again

Unresolved decisions: None

Action Items:

- schedule a labeling meeting 3rd week of September; all disciplines will have to participate
- request information on the status of clinical audits

S

Minutes Preparer

S

Concurrence, Chair

U.D.
9/21/99

APPEARS THIS WAY
ON ORIGINAL

cc:

Original NDA

HFD-580/DivFile

HFD-580/Rumble/Mercier

HFD-580/Rarick/Mann/Allen/Hixon/Jordan/Rhee/Lin/Parekh/Chatterjee/Kammerman

drafted: September 1, 1999

concurrence: Rumble 9.3.99/Lin9.7.99/Mann9.7.99/Hixon9.8.99/Chatterjee9.10.99

final: September 21, 1999

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

DUPLICATE



Pharmacia & Upjohn

NEW DRUGS

110

7000 Regage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

Office of:
P.K. Narang, Ph.D., F.C.P.
Liaison Director, New Drugs
Regulatory Affairs

Telephone No. (616) 833-9896
Facsimile No. (616) 833-8237

August 26, 1999

Lisa Rarick, M.D.
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 20-874
Lunelle™ Monthly Contraceptive Injection
(Medroxyprogesterone acetate and Estradiol cypionate
Injectable Suspension)

General Correspondence
(Impurity—Specification for Drug Product)

Dr. Rarick

On August 29, 1997 Pharmacia and Upjohn (P&U) amended their Drug Master File for _____ (an active) to add an 'impurity specification' in the ICH format in anticipation of the submission of the above NDA (# 20-874; original application was made Sept 25, 1997). This communication is provided under Attachment A. Within this, the attachment no. 1 (page 3) denotes the proposed addition to Registration Specifications.

The original NDA for Lunelle Monthly Contraceptive Injection (previously referred to as _____) was submitted in September 1997. The NDA Item 4 contained the specifications for 'Active Drug Substance' (page 4/1/43 in volume 1.4) and 'Drug Product' (page 4/1/95; at time of release and stability Page 4/1/209 in Volume 1.4) (Attachment B).

This brief is to request approval of a minor 'correction' to our original NDA. Our goal is to address an inconsistency noted during a recent review of the specifications for one of the impurities. In the Aug 29, 1997 amendment to the DMF, P&U proposed a limit of NMT _____ for 'Impurity _____' for the active substance _____. This limit was based on batch results

from lots manufactured between Jan 1995 and Apr 1997 and shown in Attachment A. This limit is further supported by the batch results from 40 newer lots (Jan 1, 1998 through most recent) of the drug substance (Attachment C).

The same impurity _____ is monitored in the drug product as _____ with a proposed limit of NMT _____ This inconsistency _____ vs _____ in the limits of _____ (a.k.a _____), occurred because the limits for the product were set based solely on the batch data for the Lunelle _____ registration stability lots _____ These stability lots were manufactured using drug substance lots which just happened to contain low levels of _____ Our oversight was to not recognize that the same impurity could be present in the active drug substance at levels of _____

While _____ is a potential degradation product in Lunelle _____, stability data have shown no change or growth in this impurity. Therefore, we would like to propose using the same limit for this impurity in the 'drug product' as used for the 'drug substance': NMT _____. P&U would greatly appreciate correcting this oversight in the specifications for drug product to reflect the limit for _____ to be _____

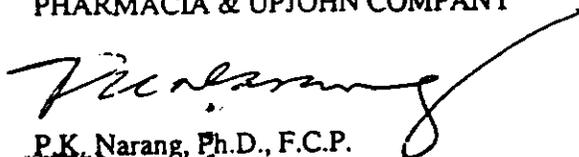
Further, the limits are in concert with the ICH Q3B guidance for reporting and identification. 'Qualification' is considered adequately established based on substantive safety data from I.M. injection marketed products containing _____ e.g., Depo-Provera Contraceptive Injection, Depo-Medrol, etc.

P&U would be delighted to have an agreement response from the reviewing Division, if possible, within one week.

If you have any questions regarding this submission, please contact me at (616) 833-9896. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY



P.K. Narang, Ph.D., F.C.P.
Director, Regulatory Affairs

PKN:

Attachments

cc: Jennifer Mercier (Desk Copy)

APPEARS THIS WAY
ON ORIGINAL

Attachment A

/S/

Teleconference Minutes SEP 7 1999

Date: August 20, 1999 **Time:** 9:30-10:30 AM **Location:** Parklawn; 17B-43

NDA 20-874 **Drug:** Lunelle™ Monthly Contraceptive Injection
(medroxyprogesterone acetate and estradiol cypionate
injectable suspension)

Indication: Contraception

Sponsor: Pharmacia & Upjohn

Type of Meeting: Information Request

Meeting Chair: Susan Allen, M.D.

External Lead: P.K. Narang

Meeting Recorder: Jennifer Mercier, B.S.

FDA Attendees:

Susan Allen, M.D. – Team Leader, Division of Reproductive and Urologic Drug Products
(DRUDP; HFD-580)

Dena Hixon, M.D. – Medical Officer, DRUDP (HFD-580)

Jennifer Mercier, B.S. – Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:

Dr. Charlie Wajszczuk, Clinical Program Leader, Clin. Development

Dr. Roger Garceau, Director, Clinical Development

Dr. P.K. Narang, Director, Global Reg. Affairs

Ms. Marie Maile, Biostatistics

Mr. Carl Deuliis, Reg. Mgr., Global Regulatory Affairs P.K. Narang – Pharmacia & Upjohn

Meeting Objective: To discuss the bleeding information presented in the NDA and the additional information needed to complete the review.

Discussion:

Table 3, page 86, vol. 1 (bleeding data)

- after 12 months use the table indicates undesirable bleeding patterns in 60% of women using Lunelle
- the sponsor needs to justify the addition of the estrogen component in the product because the table clearly does not show that the bleeding patterns have improved with this addition

Table 3.6b, Vol. 8, page 241

- the definition and criteria for “at risk for pregnancy” should be provided
- the number of patients postpartum or post-abortion who completed 15 cycles should be provided

Table 9.3, Vol. 12, page 260

- the number of patients who completed 13 or 15 cycles who used condoms during the trial should be provided
- define "not applicable" for condom use

Additional Comments

- the number of patients 35 years or older who completed 13 or 15 cycles should be provided
- the number of patients who do not fit any of the above criteria should be provided
- 3 patients used injectable contraception without the 10 month wash-out period; of those 3 patients information on how many completed 13 or 15 cycles should be provided
- of those patients who were using oral contraceptives during the 2 months prior to injection, information on how many completed 13 or 15 cycles should be provided

Decisions made:

- a table created by the Team Leader and Medical Officer will be faxed to the sponsor to complete and return with the above information
- the above information will be forwarded to the Division within a week to expedite the review

Unresolved decisions: None

Action Items:

- fax meeting minutes to sponsor within 30 days
- sponsor needs to submit the information on lipid profiles requested by the Division in June, 1999

/S/

Minutes Preparer

/S/

Concurrence, Chair

MMO 9/7/99

APPEARS THIS WAY
ON ORIGINAL

cc:

Original NDA

HFD-580/DivFile

HFD-580/Rumble/Mercier

HFD-580/Rarick/Mann/Allen/Hixon

drafted: August 25, 1999

concurrence: Hixon8.31.99/Allen9.1.99

final: September 1, 1999

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL



Pharmacia & Upjohn

ORIGINAL
ORIG AMENDMENT

BZ

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

Office of:
P.K. Narang, Ph.D., F.C.P.
Director, New Drugs
Regulatory Affairs

Telephone No. (616) 833-9896
Facsimile No. (616) 833-8237



August 6, 1999

Dr. Lisa Rarick
Director, Division of Reproductive and Urological Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-874
CYCLO-PROVERA® Contraceptive Injection
(Medroxyprogesterone Acetate and
Estradiol Cypionate Injection)

Addendum (Revision) to Clinical Study Report (/0004)

Dear Dr. Rarick

Pursuant to an internal review, Pharmacia and Upjohn informed the Division (teleconference June 22, 99) of a problem identified in the processing and reporting of some 'Safety Laboratory Data' from the pivotal clinical trial (/0004) submitted in the April 15, 1999 amendment (#001) to the NDA 20-874. This problem related to:

- Inconsistent values in the source data for the time point assigned to specimens, for some patients who completed the study, resulted in an omission of their week 60 data.
- The rule applied to handle multiple observations for the same time period chose the "worst" value instead of the value closest to the target time point in some situations, where "worst" was determined based on the difference from the normal range.
- Values not included in the week 20, 40, 60 analysis or in the index cycle analysis were not included in the patient data listings.

Following reprocessing and analysis of the corrected laboratory data, P&U is submitting this 'addendum (revision)' to the Clinical Study Report (CSR; PNU document no. a0018257) for the only pivotal clinical trial (/0004) included in the April 15, 1999 submission.

Following sections of the 'original clinical study report (CSR)' have been revised:

- Section 14.3: Clinical Laboratory Evaluations
- Section 15: Discussion
- Appendix 9A: Patient Narratives
- Appendix 9B: Lipid Profile Evaluation
- Appendix 9C: Coagulation Profile Evaluation
- Appendix 11: Data Tables for lab data
- Appendix 12: Patient Listings for lab data

To assist with the review, a table of contents (TOC) from the original report is used. Within this TOC, all revised sections have been "*italicized*". All revisions within each section, except numbers in the 'in-text tables', are "*italicized*". All in-text tables included in this addendum should be considered as 'revised'. Though page numbers are different from the original CSR, all references to sections, tables, and appendices remain unchanged.

A 'new', corrected CD-ROM with "Patient and Domain Profiles" is also provided. This 'Electronic' component conforms to the recent CDER guidance and consists of 419 MB of information. It is our belief that it should be used in-place of the one sent previously with the April 15, 1999 submission.

All data sets as 'Patient Profiles' (.pdf files) and 'Domain Profiles' (.xpt files) have been placed under the CRT directory, which has a 'Readme' file to assist with navigation. Also included is a 'Patient Profile Index' (.pdx file; created using Acrobat Catalog to allow full text search capability). The file (algor.pdf), created in Excel, provides 'algorithms' for calculated variables. The data sets included were created using SAS (version 6.08).

The enclosed transport media was checked using VirusScan NT (version 7) and deemed 'virus free'. Though P&U has taken needed precautions, use of a similar software by CDER is encouraged to confirm. The CRT directory is placed under N20874 directory, along with a copy of this letter, form 356H, and the NDA Table of Contents (included for completeness; no change). This 'Table of contents' has been hyper-linked.

Three copies of the full submission are enclosed: one each for clinical and statistical review, and one archival. Should there be any questions regarding this submission, please call me at 616 833 9896. Send all correspondence to 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Carl M. DeJulius, Jr.

P.K. Narang, Ph.D., F.C.P.
Regulatory Affairs

PKN:lmf

Attachment

REVIEWS COMPLETED	
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CSO INITIALS	DATE

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Div

MEMORANDUM

DEPARTMENT OF HEALTH AND
HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: June 2, 1999

To: Gurston Turner, Ph.D. (HFD-344)

From: Lana L. Pauls, M.P.H., Associate Director, Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Request for Clinical Inspections for NDA 20-874

15
6/11/99

In support of the above mentioned NDA for Lunelle (medroxyprogesterone acetate and estradiol cypionate), the sponsor Pharmacia and Upjohn has submitted the results of the following pivotal protocols for the indications identified below:

Indication	Pivotal Protocol #	Investigator's Name/Address
Contraception	/0004	[Redacted]
Contraception	/0004	[Redacted]
Contraception	/0004	[Redacted]

We have discussed this application with Gurston Turner and, as a result, identified the above protocols/sites for inspection.

We request that the inspections be performed and the Inspection Summary Results be provided by September 30, 1999. We intend to make a regulatory decision on this application by October 2, 1999.

Should you require any additional information please contact Jennifer Mercier, Project Manager at 301-827-4250.

Distribution: NDA 20-874
HFD-580/Division File
HFD-580/Mercier/Rumble
HFD-344/CIB Reviewer

S

APPEARS THIS WAY
ON ORIGINAL

Meeting Minutes

Date: May 21, 1999 **Time:** 12:30-1:00 PM **Location:** Parklawn; 12A-43

NDA 20-874 **Drug:** Lunelle™(medroxyprogesterone acetate and estradiol cypionate)

Indication: Contraception

Sponsor: Pharmacia and Upjohn

Type of Meeting: Status and Review Meeting

Meeting Chair: Lisa Rarick, M.D.

Meeting Recorder: Jennifer Mercier, B.S.

FDA Attendees:

Lisa Rarick, M.D. – Director, Division of Reproductive and Urologic Drug Products (DRUDP);
HFD-580

Marianne Mann, M.D. – Deputy Director, DRUDP (HFD-580)

Susan Allen, M.D. – Team Leader, DRUDP (HFD-580)

Dena Hixon, M.D. – Medical Officer, DRUDP (HFD-580)

Ameeta Parekh, Ph.D. – Team Leader, Office of Clinical Pharmacology and Biopharmaceutics II
(OCPBII) @ DRUDP (HFD-580)

Johnny Lau, R.Ph., Ph.D. – Biopharmaceutics Reviewer, OCPBII @ DRUDP (HFD-580)

David Lin, Ph.D. – Chemist, Division of New Drug Chemistry II (DNDCII) @ DRUDP (HFD-580)

Terri Rumble – Chief, Project Management Staff, DRUDP (HFD-580)

Jennifer Mercier, B.S. – Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss the completeness and acceptability of this resubmission.

Decisions made:

Clinical

- This response to the NA letter deficiencies appears complete
- Data from the original NDA submission will be used to assess safety related to coagulation parameters
- the lipid study data will have to be reanalyzed, removing the patients that were on oral contraceptives at baseline

Chemistry

- application is complete for resubmission review
- Lunelle™ Once A Month Contraceptive will need a tradename review by the LNC

Biopharmaceutics

- application is complete for resubmission review

Unresolved decisions: None

Action Items:

- communicate information needed to complete review (Biopharmaceutic comments and clinical comments)
- Chemist will request LNC review of the tradename

/S/

Minutes Preparer

/S/

6/15/99
Concurrence, Chair

Original NDA
HFD-580/DivFile
HFD-580/PM/Rumble/Pauls/Mercier
HFD-580/Rarick/Mann/Hixon/Slaughter/Allen/Lin/Rhee/Lau/Parekh

drafted: June 2, 1999/JM
concurrence: Rumble/June 7, 1999
final: June 15, 1999

MEETING MINUTES

APPEARS THIS WAY
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Pharmacia & Upjohn

ORIGINAL
NEW CORRESP
NC

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Office of:
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Director, New Drugs
Regulatory Affairs

Telephone No. (616) 833-9896
Facsimile No. (616) 833-8237

April 27, 1999

Dr. Lisa Rarick
Director, Division of Reproductive and Urological Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-874
CYCLO-PROVERA® Contraceptive Injection
(Medroxyprogesterone Acetate and
Estradiol Cypionate Injection)

New (Correct) CD-ROM's

Dear Dr. Rarick

On April 15, 99 Pharmacia and Upjohn (P&U) submitted to the agency our Amendment 001 (complete response to the deficiency letter dated September 25, 1998) which included Items 11 and 12 electronically on a CD-ROM as transport media. Earlier this week we recognized that one of the files (algor.pdf), an Excel file with algorithms for 'calculated variables' was incorrect.

Per guidance from the Project Manager (Ms. Jennifer Mercier; April 27, 1999), P&U is pleased to enclose two new copies of 'CORRECTED' CD-ROM which should replace the original ones sent with the amendment. The 'Electronic' component of this submission conforms to the recent CDER guidance (January 1999). The CD-ROM provided consists of 600 MB of information.

If you have any questions regarding the contents of this submission, please contact P.K. Narang (616) 833-9896. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

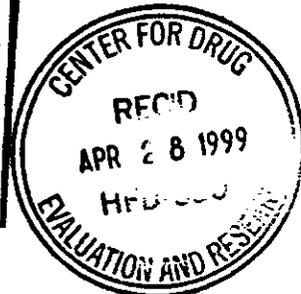
Carl M. Desjardis, Jr.

P.K. Narang, Ph.D., F.C.P.
Regulatory Affairs

PKN:mlw

cc: Ms. Jennifer Mercier (Project Manager)
FAX Copy of the letter: 301 827 4267

REVIEWS COMPLETED
CSO ACTION:
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CSO INITIALS
DATE



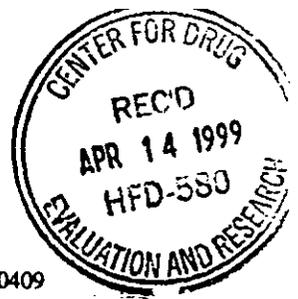


Pharmacia & Upjohn

ORIGINAL

NEW CORRESP

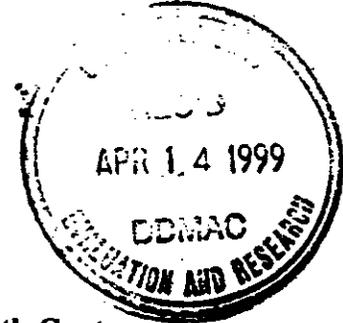
P.K. Narang, Ph.D., F.C.P.
Director, New Drugs
Regulatory Affairs
Telephone No. (616) 833 9896
Facsimile No. (616) 833 0409



April 12, 1999

ORIGINAL

Christina Kish
Division of Reproductive and Urological Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



The names have been submitted to the LNC. DTC 4/20/99

RE: NDA 20-874
Lunelle™ Once-A-Month Contraceptive
(Medroxyprogesterone Acetate and Estradiol Cypionate Injection)

pl. note 4/22/99

General Correspondence

Dear Christina

On Feb 24, 99, Pharmacia and Upjohn (P&U) had submitted for review by the Labeling and Nomenclature Committee (LNC) the following trademark and the preferred noun.

LUNELLE™ Once-A-Month Contraceptive

Following the communication you received from David Lin of the Division, you informed us during our tele-conversation (Mar 30, 99) that the LNC deemed the chosen noun 'inappropriate'. Several groups P&U continue to have (and have expressed) concerns regarding the potential confusion with the Depo-Provera Contraceptive Injection (only injectable contraceptive on the market, given every 3 months). The apparent concern stems from P&U's desire to ensure that both the prescribers and users clearly understand that the dosing regimens are different for Depo-Provera and Cyclo-Provera (LUNELLE).

Market research suggests familiarity of Physicians with Depo-Provera (dosed quarterly). As LUNELLE is also an injectable contraceptive, it is perceived by many to have similar regimen (even though they realize that it contains, in addition to a progestagen, an estrogen). Depo-Provera® has a street name "the _____" among teenagers and clinic customers. P&U believes that simply having two different trademarks (Depo-Provera and LUNELLE) for two different injectables may not suffice. As LUNELLE would be the only 'Once-a-month contraceptive' on the market, the proposed noun does not give P&U any special advantage over the competition, but clearly keeps the consumers' interest in perspective.

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA

Telephone (616) 833-4000

REVIEWS COMPLETED	
CSO ACTION:	
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4/23/99	
CSO INITIALS	DATE

P&U would like to minimize for the health care providers any confusion that LUNELLE could be administered quarterly, thus impacting the primary efficacy for the end-user. To insure that this does not happen, P&U would request LNC to reconsider the noun as stated above; or advise if one of the following could be adopted.

LUNELLE™ Once-a-Month Injectable Contraceptive

or

LUNELLE™ Monthly Contraceptive Injection

or

LUNELLE™ Contraception For One Month

May we ask for your indulgence once again, and get a quick read from the LNC. We are scheduled to file the amendment to our NDA (20-874) by April 15, 99. If there are any questions, please contact me at 616 833 9896. Send correspondence to 0635-298-113.

Sincerely,



P.K. Narang, Ph.D., F.C.P.

Director

PKN:lmf

cc : FAX a copy 301 827 4267

APPEARS THIS WAY
ON ORIGINAL



Pharmacia & Upjohn

ORIGINAL

NEW CORRESP

P.K. Narang, Ph.D., F.C.P. *NC*
Director, New Drugs
Regulatory Affairs
Telephone No. (616) 833 9896
Facsimile No. (616) 833 0409

*This name is not acceptable to the LNC.
151
3/9/99*

February 24, 1999

Lisa Rarick, M.D.
Division of Reproductive and Urological Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 20-874
Lunelle™ Once-A-Month Contraceptive
(Medroxyprogesterone Acetate and
Estradiol Cypionate Injection)

AT 3/0/99

General Correspondence

Dear Dr. Rarick:

Pharmacia and Upjohn (P&U) appreciates the promptness of the official communication from the Division dated January 27, 1999 informing us of the acceptability of the proposed tradename LUNELLE to the Labeling and Nomenclature Committee (LNC). P&U seeks LNC's indulgence to clarify use of this name with the preferred noun and any subsequent guidance regarding the acceptability of its use as noted below:

LUNELLE™ Once-A-Month Contraceptive

We sincerely apologize for not clarifying it earlier. Our preference for this noun stems from the fact that using 'Injectable Contraceptive', as for DEPO-PROVERA, might be suggestive of a similar regimen. P&U would appreciate a prompt review. If you have any questions regarding this submission, please contact P.K. Narang at 616 833 9896. Please send any correspondence to Unit 0635-298-113.

Sincerely,

P.K. Narang
P.K. Narang, Ph.D., F.C.P.
Director

PKN/crdt: Attachment

cc: Ms. Christina Kish (+ FAX : 301 827 4267)

REVIEWS COMPLETED	
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<input checked="" type="checkbox"/> LETTER	<input checked="" type="checkbox"/> N.A.T.
CSO INITIALS <i>[Signature]</i>	
DATE <i>4/21/99</i>	

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA

Telephone (616) 833-8000

BEST POSSIBLE COPY

/S/

NDA 20-874

JAN 27 1999

Pharmacia & Upjohn
Attention: P.K. Narang Ph.D., F.C.P.
Liaison Director, Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 49001

Dear Dr. Narang:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tradename Contraceptive Injection (medroxyprogesterone acetate and estradiol cypionate injectable suspension).

We also refer to your submission dated November 4, 1998, in which you submitted the proposed tradename "Lunelle".

We have received the decision from the Labeling and Nomenclature Committee and your proposed tradename is acceptable.

If you have any questions please contact Ms. Christina Kish at (301) 827-4260.

Sincerely,

/S/

1/25/99

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

Orig. NDA

HFD-580

HFD-580/DLin/MRhee

HFD-580/CKish/1.21.99/n20874.gc

Concurrence:DLin 1.22.99/MRhee 1.22.99/MMann 1.22.99

GENERAL CORRESPONDENCE (GC)

Teleconference Meeting Minutes

Date: January 26, 1999 Time: 3:00 PM - 3:30 PM Location: Parklawn 17-45

NDA 20-874 Drug Name: _____ (medroxyprogesterone acetate and estradiol cypionate) Injection

External Participant: Pharmacia and Upjohn

Type of Meeting: guidance

Meeting Chair: Susan Allen, M.D.

External Participant Lead: P.K. Narang, Ph.D.

Meeting Recorder: Christina Kish

FDA Attendees:

Susan Allen, M.D. - Medical Officer, Division of Reproductive and Urologic Drug Products (DRUDP;HFD-580)

Christina Kish - Project Manager, DRUDP (HFD-580)

External Constituents:

P.K. Narang, Ph.D. - Director, New Drugs, Regulatory Affairs

Meeting Objectives:

To discuss the sponsor's minutes of the November 13, 1998, teleconference.

Discussion Points:

- Background

- a teleconference was held with the sponsor November 13, 1998
- the sponsor's current clinical trial was the subject of that discussion
- issues were raised regarding specific criteria required to ensure that acceptable data was submitted in response to the not approvable letter previously issued to the sponsor for their application
- the sponsor faxed a copy of their minutes to this meeting on December 1, 1998

- Discussion

- upon review of the sponsor's minutes, it was determined that one point was not reflected accurately
- under the subsection "Conclusions" the sponsor had written the following statement (*italics are this writer's*):

"They (*the FDA*) did verify that it was permissible to close the study early if we (*the sponsor*) were willing to take the risk that all requirements for a pivotal, multicenter safety and efficacy study as outlined in the deficiency letter (Sept 25, 1998) would be met or adequately/rationally addressed."

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(medroxyprogesterone acetate and estradiol cypionate) Injection
January 26, 1999

- DRUDP clarified with the sponsor that, as stated on Page 1 of the sponsor's draft minutes from the November 13, 1998, teleconference, all deficiencies in the not approval letter for this product would need to be met
- the sponsor was advised that their decision to close the study early had been unexpected because it was envisioned that in order to obtain sufficient numbers of subjects who met acceptable entrance criteria the sponsor might have to prolong the study
- the Division acknowledged that if specific information, typically required, may not have been captured in the study (i.e., sexual activity throughout the study period) the sponsor should justify why this information would not be required to determine efficacy
- the sponsor intends to submit a complete response in March 1999
- the Division stated that it would be helpful to receive the efficacy and safety summary on disk and in addition for the sponsor to submit electronically a very detailed summary of the current clinical study, summaries of the clinical pharmacology studies and complete case report forms for every subject who became pregnant in the study
- the sponsor suggested hyperlinking study reports to the appropriate tables and was told that would be acceptable

Decisions Reached:

- the sponsor should revise their minutes as discussed above
- the sponsor is encouraged to submit study information electronically when submitting their complete response

Unresolved Issues: none

Action Items: none

Minutes Preparer

2/16/99

Concurrence, Chair

MMO
2/16/99

cc:
Orig. IND
HFD-580
MEETING ATTENDEES
HFD-580/CKish/1.27.99/n20874.tc3
Concurrence:SAllen 2.16.99

APPEARS THIS WAY
ON ORIGINAL

MEETING MINUTES

DF

Memorandum

To: NDA 20-874, Medroxyprogesterone acetate and estradiol cypionate Injection
Through: Moo-Jhong Rhee, Ph.D. S 1/22/99
From: David Lin, Ph.D. S 1/22/99
Date: January 22, 1999
Re: Review of Sponsor's Tradename Submission (04-NOV-1998)

The sponsor has submitted tradename, Lunelle, to replace Lunelle was submitted to the Labeling and Nomenclature Committee for review on November 10, 1998, and determined to be acceptable on January 19, 1999 (see attachment).

cc:
 Orig. NDA #20-874
 HFD-580/Division File
 HFD-580/CKish
 HFD-580/MRhee/DLin

R/D Init by: MJ Rhee

Filename: nda20874.4 (doc)

APPEARS THIS WAY
 ON ORIGINAL

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D.U. File

Teleconference Meeting Minutes

Date: November 13, 1998 **Time:** 2:00 PM - 2:30 PM **Location:** Parklawn C/R 17B-43-

NDA 20-874 **Drug Name:** _____ (medroxyprogesterone acetate and estradiol cypionate) Injection

External Participant: Pharmacia and Upjohn

Type of Meeting: guidance

Meeting Chair: Marianne Mann, M.D.

External Participant Lead: P.K. Narang, Ph.D.

Meeting Recorder: Christina Kish

FDA Attendees:

Marianne Mann, M.D. - Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP;HFD-580)

Susan Allen, M.D. - Medical Officer, DRUDP (HFD-580)

Julian Safran, M.D. - Medical Officer, DRUDP (HFD-580)

Christina Kish - Project Manager, DRUDP (HFD-580)

External Constituents:

Roger Garceau, M.D. - Clinical Development

Charlie Wajszczuk, M.D. - Clinical Development

Henk De Koning Gans, M.D. - Project Leader

P.K. Narang, Ph.D. - Director, New Drugs, Regulatory Affairs

Nancy Busso - Regulatory Affairs

Diane Beuving - Project Manager

Matt Cromie - Clinical Trials Specialist

Meeting Objectives:

To discuss the sponsor's proposal with regard to a response to the clinical deficiencies listed in the not approval letter issued for this product on September 25, 1998.

Discussion Points:

- Background
 - the sponsor intends to utilize their U.S. clinical trial to respond to the deficiency letter of September 25, 1998
 - the sponsor proposes terminating the study 4 weeks earlier than planned
 - a complete response to the not approval letter is expected in early April, 1999

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(medroxyprogesterone acetate and
estradiol cypionate) Injection
November 13, 1998

- **Early Termination of Clinical Trial**
 - the sponsor is taking a risk in stopping the study ahead of schedule
 - every point in the deficiency letter must be addressed
 - the sponsor is confident that they can respond to each parameter outlined in the not approval letter, despite the fact that some women previously taking an injectable contraceptive had a washout period of only eight months as opposed to the 10 months required in the not approval letter
 - the sponsor questioned how the 10 month wash out period was derived and were told that this was for safety concerns and that a literature citation could be provided upon request; the sponsor did not request the citation

- **Mishandling of Blood Samples**
 - aliquots of baseline blood samples were sent to a specific laboratory for coagulation studies
 - an as yet undetermined number of samples were left at room temperature prior to assay, resulting in abnormal laboratory values for baseline coagulation parameters
 - abnormal values due to mishandling occurred in both study arms
 - the sponsor will submit those laboratory tests that they consider valid
 - the sponsor is encouraged to submit data on coagulation values from other supporting clinical trials

- **Safety Data Submission**
 - the sponsor proposes submitting only serious or unexpected adverse events in the complete response
 - the sponsor must submit all adverse events which occurred in the U.S. clinical trial

- **Safety Update Waiver**
 - the sponsor requested that a waiver be granted for the Safety Update to the complete response submission
 - the request for waiver is denied, the sponsor should submit all information available to them in a safety update, this update may be submitted at month 2, 3 or 4 during the review cycle
 - it was explained to the sponsor that the U.S. trial needs to be as complete as possible to address all the deficiencies noted in the previous NDA not approval letter

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(medroxyprogesterone acetate and estradiol cypionate) Injection
November 13, 1998

Decisions Reached:

- the sponsor may terminate the clinical study early if they are confident that they will meet all the deficiencies listed in the not approval letter
- the sponsor must meet every deficiency and study parameter listed in the not approval letter, further leeway from the not approval letter will not be permitted
- the sponsor will submit a complete response in April 1999
- the sponsor may use coagulation values from other clinical trials

Unresolved Issues: none

Action Items: see decisions reached

S

S

Minutes Preparer

11/15/98

Concurrence, Chair

11/19/98

cc:

Orig. IND

HFD-580

MEETING ATTENDEES

HFD-580/CKish/11.13.98/n20874.tc2

Concurrence: JSafran 11.16.98/SAllen 11.18.98

MEETING MINUTES



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Pharmacia Upjohn



Office of: NEW-CORRESP

P.K. Narang, Ph.D., F.C.P.
Liaison Director, New Drugs
Regulatory Affairs

Telephone No. (616) 833 9896
Facsimile No. (616) 833 0409

November 4, 1998

Division of Reproductive and Urological Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

*Submitted to LNC on
11/10/98 151
11/12/98*

151 11/13/98

RE: NDA 20-874
LUNELLE™ Monthly Contraceptive
(medroxyprogesterone acetate and
estradiol cypionate Injection)

General Correspondence

Dear Sir/Madam:

Pharmacia and Upjohn (P&U) wishes to submit the tradename/proprietary name LUNELLE™ to the Labeling and Nomenclature Committee for review. This would replace Cycle-Provera submitted previously but deemed inappropriate by the agency and withdrawn by P&U. We would appreciate a prompt review, preferably at the next upcoming committee meeting at the end of this month.

Should you have any questions, please contact me at (616) 833-9896. Please send any correspondence to Unit 0635-298-113.

Sincerely,

P.K. Narang, Ph.D., F.C.P.
Liaison Director

PKN:SEH

cc: Ms. Christina Kish

REVIEWS COMPLETED
CSO ACTION: <input type="checkbox"/> LETTER <input checked="" type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS <i>[Signature]</i> DATE <i>[Signature]</i>



NEW CORRESP

ORIGINAL

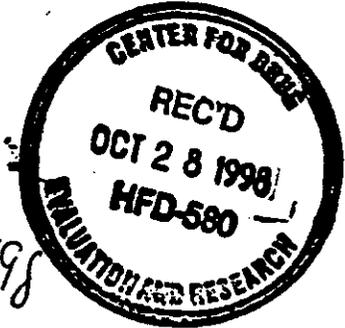
Pharmacia & Upjohn

P.K. Narang, Ph.D., F.C.P.
Director, New Drugs
US - Regulatory Affairs
Telephone No. (616) 833 9896
Facsimile No. (616) 833 8237

October 26, 1998

Telecon held w/ 9/21/98

Lisa Rarick, M.D.
Division of Reproductive and Urological Drug Products (HFD-580)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



11/14/98

REVIEWS COMPLETED
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DATE

RE: NDA 20-874
CYCLO-PROVERA Contraceptive Injection
(medroxyprogesterone acetate and estradiol cypionate injection)

General Correspondence

Dear Dr. Rarick:

In our correspondence of October 1, 1998, Pharmacia & Upjohn (P&U) notified you of our intent to file an amendment to NDA 20-874 for CYCLO-PROVERA Contraceptive Injection in response to deficiencies noted in the 'NDA action letter' dated September 25, 1998.

Per our earlier teleconference, to provide 'complete response', P&U intends to rely on new clinical data from the ongoing, adequate and well-controlled US study entitled "CYCLO-PROVERA Contraceptive Injection: A Comparative Study of Safety, Patient Acceptability and Efficacy to Ortho-Novum 7/7/7 28 tablets" (Protocol: 0004). This study has enrolled 782 women in the CYCLO-PROVERA (C-P) and 321 women in the Ortho-Novum (O-N) arms.

Having completed an in-depth assessment of the noted deficiencies, we wish to share with you our proposal and some key items for which your guidance is sought. Our own assessment has focused on desired submission plans, patient accrual/completion dates, and possible impact on risk:benefit assessment.

Amendment Proposal for NDA 20-874: CYCLO-PROVERA

Efficacy Issues

Should the ongoing 15 cycle pivotal trial continue, the last patient follow-up visit would be expected around mid April 1999. P&U wishes to cut-off study drug administration on December 31, 1998 (last injection for C-P and first tablet for O-N). Follow-up will continue for the next 30 days when the study would be closed (as of January 31, 1999). Women

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA

Telephone (616) 833-4000

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starting or continuing hormonal contraception prior to the 30 days will be followed up through the day of receipt of their first dose of continued therapy. Projections show that the premature closure censor only four women in the C-P group (only one of whom may not complete 52 weeks). Given the projected drop-out rates (and January 31, 99 closure), we envision providing a database (>8500 follow-up cycles on C-P and >12,000 total; see Table 1 below) to allow a robust assessment of safety/efficacy and risk:benefit for C-P. We project this database to have >325 women on C-P treatment for the planned duration (60 weeks).

As you are aware, the original protocol did not require monthly pregnancy testing. Per your guidance, an amendment (Serial no. 019, August 11, 1998) for monthly pregnancy testing was implemented by P&U as of August 1, 1998 to collect information deemed vital to supplement efficacy data. It is anticipated that pregnancy test data at final follow-up would be available in >500 women and in >90% of women completing 60 weeks (C-P arm).

TABLE 1: Cohort Estimates US Trial (/0004): Comparison of CYCLO-PROVERA vs. Ortho-Novum 7/7/7 (28 days)

COHORT SIZE ESTIMATES	C-P	O-N 7/7/7	Total
- Enrolled ^a	782	321	1103
By Jan 31, 1999 Study Closure^b			
- Completing 60 weeks	360	160	520
- Censored by premature closure ^c	4	23	27
- Total Number F/U Cycles Expected	8700	3700	12,400
- Using injectable contraceptive (<10 mo washout)	8	0	8
- Post-abortion and Post-partum ^d	100	15	115
- In-study on August 1, 1998 ^e	380	190	570
- Pregnancy Tests (%) for each of the first 10 cycles	19%	10%	-
- Pregnancy Tests (%) at week 60	96%	93%	-
- Pregnancy Tests at final F/U	610	250	860

^a Actual

^b Last administration (C-P injection or first O-N tablet) December 31, 98.

Numbers in this section have been estimated assuming projected drop-out rates.

^c All except 2 women (1 in each arm) expected to complete 52 weeks.

^d Majority expected to have regular period within 35 days of treatment initiation.

^e Women with monthly pregnancy testing for remainder of study duration. Those with no pregnancy test at exit as of August 1, 1998 being queried on pregnancy status since discontinuing.

All others should have a pregnancy test at final visit.

Safety Issues

The safety analysis from pivotal protocol /0004 would address uterine bleeding pattern changes and other variables noted in the 'deficiency letter'. Given agency's concerns with the data collection provisions and the quality of the older WHO trials, we propose to not integrate safety data from WHO studies with data from the well-controlled US trial.

One issue that we wish to bring to your attention deals with the early results of some coagulation tests. The US study protocol (0004) planned to investigate the effects on coagulation in a subset of patients for both — and O-N. We have been advised by the 'central laboratory' performing these tests that a relatively large number of baseline blood samples were improperly handled. This has led to abnormalities in the early results of some tests. Other tests have not yet been performed, but it is expected that anomalous results may also occur for these as well. We continue to assess the extent of the problem and would like to discuss with you possible contingency plans to provide needed data to fulfill the requirements noted in agency's deficiency letter.

Safety Reporting from Other Clinical Studies

For study — (extension protocol following 0004, which has only 68 women as of October 14, 1998) and study 0009 (in adolescents; expected to start late November 1998), we will provide in the amendment a list of *only* those events considered 'serious' or 'unexpected'. However, P&U will ensure due consideration to any event deemed clinically relevant from these and previously submitted WHO trials while formulating the proposed label.

Further, we wish to request a 'waiver' from submitting the 4-month NDA safety update from ongoing non-pivotal studies — and 0009.

General

If this proposal were to be acceptable, P&U would anticipate submitting the 'NDA amendment' in early April 1999. This amendment will primarily encompass complete data from one pivotal, multicenter safety (and efficacy) trial (study 0004), and new kinetic data assessing impact of various drug administration sites, body mass index (study 0004), and relationship of drug concentration to 'ovulation return' (study 0006).

Pursuant to your review of this proposal, P&U would appreciate having an opportunity to discuss this proposal, possibly via a telecon, along with other issues should any become apparent in the meantime. We anxiously look forward to hearing from you at your earliest convenience regarding the telecon timing (hopefully in the next two weeks), to allow ourselves to start finalizing our plans. Should you have any questions, please contact me. Please send any correspondence to Unit 0635-298-113.

Best regards!

Sincerely,



P.K. Narang, Ph.D., F.C.P.
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

PKN/crdt:Attachment

cc: Ms. Christina Kish (FAX Letter : 301 827 4267)



Pharmacia & Upjohn

ORIGINAL

NEW CORRESP

AJ 10/26/98

Office of:
P.K. Narang, Ph.D., F.C.P.
Liaison Director, New Drugs
Regulatory Affairs

Telephone No. (616) 833-9896
Facsimile No. (616) 833-8237

noted
DTL
10/22/98

October 1, 1998

Lisa Rarick, M.D.
Division of Reproductive and Urological Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

noted
10/14/98



RE: NDA 20-874
CYCLO-PROVERA Injection
(Medroxyprogesterone Acetate and
Estradiol Cypionate Injection)

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input checked="" type="checkbox"/> R.A.I. <input type="checkbox"/> MEMO
CSO INITIALS: [Signature]
DATE: 10/26/98

General Correspondence
Response to FDA Action Letter
(Sept 25, 1998)

Dear Dr. Rarick

In response to the NDA 'action letter' dated September 25, 1998, per available options under 21 CFR 314.120(a), Pharmacia and Upjohn (P&U) would like to notify you of its intent to file an amendment to the above NDA to address noted deficiencies. P&U is also cognizant of the extension of the review period per 21 CFR 314.60.

To respond to the clinical deficiencies, P&U intends to provide new clinical data from an ongoing, adequate, and well-controlled US study entitled "CYCLO-PROVERA Contraceptive Injection: A Comparative Study of Safety, Patient Acceptability and Efficacy to Ortho-Novum 7/7/7 28 tablets" (Protocol M/5615/0004). This study has enrolled 782 women in the CYCLO-PROVERA and 320 women in the Ortho Novum 7/7/7 arms.

We anticipate submitting the amendment to the NDA, providing 'complete response' to the action letter, in late March/early April 1999. We look forward to keeping the division appraised of our progress.

If you have any questions regarding this submission, please contact me at (616) 833-9896. Please send any correspondence to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN CO.



P. K. Narang, Ph.D., F.C.P.
Liaison Director
Regulatory Affairs

PKN:kmv

cc: Ms. Christina Kish (FAX Letter : 301 827 4267)

APPEARS THIS WAS
ON ORIGINAL

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 20-874

Food and Drug Administration
Rockville MD 20857

Pharmacia & Upjohn
Attention: P.K. Narang Ph.D., F.C.P.
Liaison Director, Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 49001

SEP 25 1998

Dear Dr. Narang:

Please refer to your new drug application (NDA) dated September 25, 1997, received September 26, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tradename Contraceptive Injection (medroxyprogesterone acetate and estradiol cypionate injectable suspension).

We acknowledge receipt of your submissions dated November 24 and December 12, 1997; and March 4, May 21, June 5, 29 (2), and 30, July 15, 16 and 28, and August 7 and 13, 1998. We also acknowledge receipt of your submission dated August 11, 1998. This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

The user fee goal date for this application is September 26, 1998.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The trials submitted in support of this application contain insufficient information to support either the safety or efficacy of this product.

The deficiencies include the following:

Data collection for safety assessments was inadequate and treatment of bleeding-related events during the pivotal trials confounded the results obtained for menstrual bleeding pattern changes associated with use of this drug. Routine monitoring of hemoglobin (Hg) and hematocrit (HCT) was not performed throughout any of the pivotal trials making it impossible to calculate the true incidence of anemia resulting from the use of this drug.

The quality of the efficacy data obtained from the pivotal trials was compromised. The lack of information available on specific patient populations who might not have been at risk of pregnancy at enrollment as well as the lack of adequate pregnancy testing for method failure-assessment made interpretation of the efficacy data difficult. In addition, several of the products used for treatment of bleeding disturbances could have affected efficacy results.

Sufficient records for auditing to verify data collection and adherence to the study protocol were available for only 2 of the 44.

A trial that includes appropriate patient numbers, data collection records (including case report forms and source documents) and efficacy monitoring is needed to address the deficiencies in your application. Specifically, this trial should fulfill the following criteria:

Efficacy

- ✓1. The trial should provide data on a minimum of 200 subjects completing 13 cycles of product use with pregnancy tests at study discontinuation (minimum requirement) and/or at monthly intervals (preferred).
- ✓2. Along with usual inclusion/exclusion criteria, the following criteria should apply for these 200 women:
 - a. subjects must be in a heterosexual relationship and at risk for pregnancy;
 - b. subjects enrolled post-abortion and post-partum should have experienced at least one normal menstrual period prior to initiation of treatment; and
 - c. subjects using injectable contraceptives should have a washout period of at least 10 months prior to enrollment.
- ✓3. If emergency contraception is allowed, provide a data analysis plan that incorporates this use.
- ✓4. Life table pregnancy rates as well as a Pearl Index should be calculated as measures of failure rates during the trial.
5. Analyses of data (both efficacy and safety) stratified by body mass index should be provided.

Safety

- ✓1. Plans for management and analyses of bleeding disturbances during the trial should be described.
2. Data on the following parameters following one year of study drug exposure should be submitted:
 - ✓a. lipids;
 - ✓b. serum glucose/carbohydrate metabolism;
 - ✓c. blood pressure;
 - ✓d. hepatic function;
 - ✓e. weight change (expressed in increments of 5 pounds);
 - ✓f. body mass index (BMI);
 - ✓g. coagulation factors; and
 - ✓h. Hg and HCT.
- ✓3. Complete information on bleeding pattern changes over a one-year period of study drug use should be submitted.
- ✓4. Additionally, any data regarding return to fertility, *in utero* exposure (e.g., pregnancy outcome information) and lactation should be submitted for review.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Christina Kish, Project Manager, at (301) 827-4260.

Sincerely,

/S/

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 24-Sep-1998 04:54pm EDT
From: Joseph DeGeorge
DEGEORGE
Dept: HFD-024 WOC2 6024
Tel No: 301-594-6758 FAX 301-594-5298

O: Leah Ripper (.RIPPER)
O: Joseph DeGeorge (DEGEORGE)
C: James Bilstad (BILSTAD)
C: Christina Kish (KISHC)

Subject: Re: Action Pkg

As this is an NA this is not important, but the labeling will need revision.

) No doses or comparisons of exposure (even on a basis) are provided.

) A 2 year monkey study is not an assessment of carcinogenic potential and should not be presented as such. Finding tumors would be a surprise, even for a fairly potent carcinogen, and negative findings are informative.

) There is no description of whether these drugs are excreted in milk and whether that affects the neonate and if this should be considered by nursing mother. Many women do use contraception, including hormonal treatments, while nursing.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 22-Sep-1998 11:36am EDT
From: Carol-Anne Currier
CURRIER
Dept: HFD-344 MPN1 125
Tel No: 301-827-7397 FAX 301-594-1204

TO: Leah Ripper
TO: Gurston Turner

(RIPPER)
(TURNERG)

Subject: Re: N20-874 Provera+estradiol cypionate

Lee-

There were 3 foreign sites that were originally requested for inspection by Dr. Rarick, but I believe that the sponsor could not assure us that there would be adequate records for inspection at any of the sites except the Hungarian site. That is the only site that was inspected. None others are scheduled for this NDA.

If you need to know some specifics about the inspection, you can talk with George Prager; he accompanied Gus on the inspection, otherwise Gus would be back on Friday. He is on another foreign inspection until then.

Carolanne

Can you give me a bottom line about the inspection for NDA 20-874? Is it the
>only inspection planned?
>
>Lee

APPEARS THIS WAY
ON ORIGINAL

NDA ACTION PACKAGE ROUTING RECORD

NDA # 20-874 Date Pkg Rec'd in HFD-102 9/18/98

Drug medroxyprogesterone acetate and estradiol cypionate injection

AP / AE / NA Division 580 PM C. Kish Drug Classification 4S

Date Orig NDA Recd 7/26/97 User Fee Goal Date 9/25/98

EER Expires 11/9/98 Ph 4 Commitments N/A

DSI Documentation N/A Safety Update 7/16/98

Patent Info? (Y) / N EA Completed? Y / N / (C) Debarment Certification? (Y) / N
L & N Review? Y / N FONSI in Pkg? Y / N / (NA)

New name to be submitted

Reviewer _____ Receipt _____ Action _____

L. Ripper
Associate Director
for Reg Affairs
ODE II

Date 9/18 Initials LSI

Date 9/23 Initials LSI
Returned to Division
for corrections _____
Forwarded ✓

Comments:
*Need electronic pediatric page
See comments on ltr*

J. Gibbs, Ph.D.
Director,
Div of Chemistry II

Date 9/23 Initial LSI

Date 9/23 Initials LSI
Returned to Division
for corrections _____
Forwarded ✓

Comments: EA: Qualified for categorical exclusion.
EER: Accepted 10 Nov 97 by J. D'Ambrosio (HFD-324)
TRADENAME: Applicant has committed to developing a new trademark and has withdrawn ^{Cyelo.} ~~Parvo~~
MICRO: Recommended for approval in this review with per Rev. #1 dtd 5 Mar 98.
Labeling: Acceptable except for Trademark, see above.
C.M.C.: Accepted per CR #3 dated 7/4/98 except for Trademark issue (see above).

J. DeGeorge, Ph.D.
Senior Pharmacologist/
Toxicologist, ORM

Date 9/23 Initials _____

Date 9/24 Initials _____
Returned to Division
for corrections _____
Forwarded ✓

Comments:
See 9/24 email w/ labeling comments

J. Bilstad, M.D.
Director
ODE II

Date _____ Initials _____

Date _____ Initials _____
Returned to Division
for corrections 9/24, 9/25

Letter signed _____

Division Director Memo

NDA: 20-874
Sponsor: Pharmacia and Upjohn
Drug: "Tradename" (medroxyprogesterone acetate and estradiol cypionate)
0.5mL injectable formulation
Indication: Pregnancy Prevention
Date received: September 26, 1997
Date of Memo: September 17, 1998

This product, consisting of 25 mg medroxyprogesterone acetate and 5 mg estradiol cypionate, intended as a once monthly injection for the prevention of pregnancy, is currently marketed in several Latin American and Asian countries. This once-a-month estrogen/progestin combination product offers the potential advantage of improved compliance, although similar side effect profile, as compared to once-daily combination oral contraceptives.

Three major controlled trials are submitted and reviewed. All three were performed under the sponsorship of the World Health Organization.

As assessed and summarized in the "Joint Medical Officer" review, several issues support a non-approval action at this time. The primary concerns revolve around issues of inclusion criteria used (many women enrolled may not have been at risk of pregnancy), lack of necessary pregnancy testing, high loss to follow-up as well as significant discontinuations. The trials also allowed for concurrent treatment of vaginal bleeding which could include use of other contraceptive methods.

Along with concerns regarding the ability to assess effectiveness in these trials, several concerns regarding the ability to adequately assess safety are raised in the review. Minimal safety information was collected, the information was classified retrospectively, and no CRFs are available for two of the three studies.

As is discussed in the review and correspondence, the sponsor has initiated a large phase III trial in the US. If this study can answer the concerns raised during the review of this application, this one trial may be sufficient for resubmission and review.

The non-approval letter outlines the information needed to answer the outstanding effectiveness and safety questions for this application.


Lisa Karick, MD
Director
DRUDP, HFD-580

9/17/98

APPEARS THIS WAY
ON ORIGINAL

cc: NDA 20-847
HFD-580/Allen/Safran/Mann

Group Leader Memorandum

SEP 08 1998
SEP 08 1998

NDA: 20-874
Drug: []
Medroxyprogesterone acetate and estradiol cypionate
Indication: prevention of pregnancy
Dose: 25 mg medroxyprogesterone acetate
5 mg estradiol cypionate
given once monthly
Formulation: 0.5 ml injectable solution
Related Products: Depo-Provera (marketed in the U.S.)
Mesigyna (marketed in non-U.S. countries)
Applicant: Pharmacia and Upjohn
Original Submission: 9/26/97
Review Completed: 9/1/98
Date of Memorandum: 8/28/98

Background

While there are many oral contraceptives approved for daily use on a month by month basis, the only approved injectable contraceptive in the United States (Depo-Provera®) is used every three months. Presumably, some women may be reluctant to use such injectable contraceptives due to concern that adverse events, if experienced, may last up to 3 months in duration. This NDA is for an injectable contraceptive which would be given on a monthly basis, and thus provide women with a new option. In addition, Depo-Provera® contains only progesterone, while [] contains both estrogen and progesterone components. Estrogen was added in an attempt to result in cyclical monthly bleeding patterns which are desired by some women.

The data for this NDA submission is from three major contraceptive trials performed in foreign countries by the World Health Organization. These trials were begun as early as 1984, with the Multicountry study conducted prior to the development of GCP guidelines. The three major controlled studies were:

- Multicountry Study (White, Hispanic, Asian population)
- Egypt Study (White population)
- China Study (Asian population)

Results of Studies

As per the medical officers' (Allen/Safran) review, there were many concerns regarding the data which was submitted. Briefly, these concerns included:

- There are no case report forms available from either Egypt or China. Thus, FDA was unable to verify 75% of the data in this trial. Site inspections were only possible at two of a total of 44 sites. Thus, the quality of the database was not able to be assessed.
- Enrollment criteria were inappropriate. Patients enrolled in contraceptive trials should clearly be fertile, but the _____ studies did not adequately assure this in many cases. Thus, the efficacy results obtained are based on patients who may not have been at risk for pregnancy.
- Routine pregnancy testing (the primary efficacy endpoint of interest) was not performed. Typically, trials for contraceptives include monthly visits at which pregnancy testing is performed. Most importantly, however, pregnancy testing at study discontinuation was not performed. Thus, pregnancy rates are difficult to truly establish, and may, in fact, be significantly underestimated.
- The primary safety endpoint of concern (vaginal bleeding) was not assessed adequately. Typically, patients with bleeding are followed in these trials without intervention until the problem resolves or they are discontinued after meeting an objective criteria such as anemia or the patient subjectively felt the bleeding was unacceptable. In the pivotal trials for _____, however, patients with bleeding were often treated (with iron supplements, uterotonics, vitamin K, and supplemental estrogen and progesterone) and maintained in the study. Accurate assessments of bleeding are therefore difficult to make. Moreover, the hormonal treatments given to treat bleeding may have also confounded the rate of pregnancy noted.
- Diverse patient populations reflecting the U.S. population were not studied. In particular, African-Americans were not represented in these trials.
- Safety monitoring in the Multicountry trial included only a maximum of two medical events per visit. Limiting safety monitoring in this way is clearly inappropriate, and leads to concerns that adverse events were therefore under-reported.
- Safety information for medical events was obtained retrospectively by the sponsor, who had a monitor review the data listings of medical events, and classify them as having "potential clinical relevance." This procedure clearly introduces the potential for bias.

Conclusions:

Due to the concerns described above, and those presented in the medical officers' review, the application does not support either the efficacy or safety of _____ for the prevention of pregnancy. I concur with the medical officers' conclusion that this application, therefore, is not approvable. The large scale, ongoing, trial in the United States may, however, provide information to support the efficacy and safety claims which

the sponsor desires for _____ The sponsor is therefore encouraged to submit information from the completed U.S. trial, when available, in an NDA resubmission.

5
Marianne Mann, M.D.
Deputy Director, HFD-580

9/8/98

cc:
NDA 20-847
HFD-580/Rarick/Safran/Allen/Mann

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

DRUG AMENDMENT



Pharmacia & Upjohn ^{SU}

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000



Office of:
P.K. Narang, Ph.D., F.C.P.
Liaison Director, New Drugs
Regulatory Affairs

Telephone No. (616) 833-9896
Facsimile No. (616) 833-8237

August 18, 1998

Dr. Lisa Rarick
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

*Noted
15/8/99*

RE: NDA 20-874
Lunelle™ Monthly Contraceptive
Injection (Medroxyprogesterone
acetate and Estradiol cypionate
Injectable Suspension)

SAFETY UPDATE (August 1999)

Dear Dr. Rarick:

In accordance with provisions under 21 CFR § 314.50(d)(5)(vi)(b)(1), Pharmacia and Upjohn is submitting a Safety Update Report for Lunelle™ Monthly Contraceptive Injection (medroxyprogesterone acetate and estradiol cypionate injectable suspension). This report provides safety data that have become available from three US trials (M/5415/0011 (extension of the pivotal trial /0004, M/5415/0009 and Z/5415/0012). The cut-off date for the assessments in this 'safety update' is 31 May 1999.

Appendices 6 and 7 provide associated case report forms (CRFs) for deaths (none), pregnancy (one), and drop-outs due to adverse events only in electronic format (as .pdf files). This 'Electronic' component, using CD-ROM as transport media, conforms to the recent CDER guidance and consists of approximately 5 MB of information. A copy of this cover letter, Form 356H and the Table of Contents are included on the CD. The enclosed transport media was

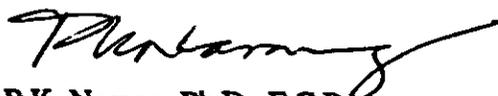
checked using VirusScan NT (version 7) and deemed 'virus free'. Though P&U has taken needed precautions, use of a similar software by CDER is encouraged to confirm.

Initially, the Division had deemed receipt of another safety update possibly relevant prior to the action letter date. Based on current evaluation of the database, P&U wishes to note that another update would at best contain two months of additional data in a small cohort (< 270 additional monthly cycles); 17 additional discontinuations (three due to non-serious AEs). There are no new reports of any serious AEs. Extremely limited amount and nature of new data is unlikely to provide substantial information to modulate estimates of safety and efficacy for this product, as assessed previously from significantly large databases for WHO studies (original NDA submission; >40,000 cycles), and pivotal US study (/0004; April 15th submission, with >8900 cycles). Therefore, P&U wishes to request a waiver from other Safety Updates prior to the action letter date and per 21 CFR § 314.50 (5) (vi) (b) (2).

Last but not the least, if acceptable to the Division, P&U would like to begin using the recent LNC approved 'Lunelle™ Monthly Contraceptive Injection' name instead of 'CYCLO-PROVERA Monthly Contraceptive Injection' on all future communications regarding this NDA. If you have any questions regarding this submission, please contact me at (616) 833-9896. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY



P.K. Narang, Ph.D., F.C.P.
Director, Regulatory Affairs

PKN:lmf

Attachments

cc: Jennifer Mercier (Project Manger) FAX: 301 827 4267

REVIEWS COMPLETED	
CSO ACTION	
<input type="checkbox"/> LETTER	<i>N</i>
CSO INITIALS	<i>ES</i>
	<i>BAPE</i>

*Noted.
Considered in NDA
Review 9/1/99
T.S!*



Pharmacia & Upjohn

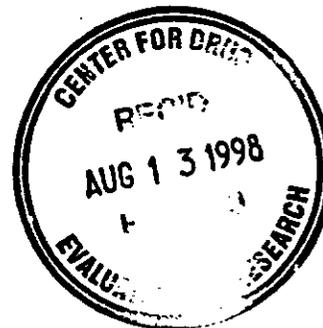
ORIGINAL

P.K. Narang, Ph.D., F.C.P.
Liaison Director, New Drugs
Regulatory Affairs
Telephone No. (616) 833 9896
Facsimile No. (616) 833 0409

August 13, 1998

SUPL NEW CORRESP

Lisa Rarick, M.D.
Division of Reproductive and Urological Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

RE: NDA 20-874

Injection
(Medroxyprogesterone Acetate and
Estradiol Cypionate Injection)

General Correspondence

Dear Dr. Rarick:

Per the August 5, 1998 request from Ms. C. Kish, Project Manager, a modified 'Debarment Certificate' for the NDA 20-874 is attached.

Should you have any questions, please contact me at 616-833-9896. Please send any correspondence to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

P.K. Narang, Ph.D., F.C.P.
Liaison Director

PKN/crdt

Attachment

cc: Ms. Christina Kish

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE



Pharmacia & Upjohn ORIGINAL

P.K. Narang, Ph.D., F.C.P.
Liaison Director, New Drugs
Regulatory Affairs
Telephone No. (616) 833 9896
Facsimile No. (616) 833 0409

August 12, 1998

SUPL NEW CORRESP

Lisa Rarick, M.D.
Division of Reproductive and Urological Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



*noted
151
9/19/98*

RE: NDA 20-874
CYCLO-PROVERA Injection
(Medroxyprogesterone Acetate and
Estradiol Cypionate Injection)

General Correspondence

*Noted
151
9/21/98*

Dear Dr. Rarick:

Pharmacia and Upjohn wishes to withdraw from any further regulatory considerations the trademark _____ (initially proposed for Cyclo-Provera in submission 'General Correspondence' of June 29, 1998). We sincerely apologize for any inconvenience this change may cause. P&U intends to submit an 'alternative trademark' for review by the Nomenclature Committee in the very near future.

If you have any questions regarding this submission, please contact P.K. Narang at (616) 833-9896. Please send any correspondence to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY.

P.K. Narang, Ph.D., F.C.P.
Liaison Director

PKN/crdt:Attachments

*Noted
151
9/22/98*



151 9/15/98

cc: Ms. Christina Kishi (FAX : 301 827 4267)

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA

Telephone (616) 833-4000

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Pharmacia & Upjohn

P.K. Narang, Ph.D., F.C.P.
Liaison Director, New Drugs
Regulatory Affairs
Telephone No. (616) 833 9896
Facsimile No. (616) 833 0409

August 11, 1998

Lisa Rarick, M.D.
Division of Reproductive and Urological Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-874
CYCLO-PROVERA Contraceptive
Injection (Medroxyprogesterone
Acetate and Estradiol Cypionate
Injection)

General Correspondence

Dear Dr. Rarick:

Pharmacia and Upjohn appreciates the concerns expressed by the Division's Medical Reviewers previously and during the last telecon (August 4, 1998) regarding the need for pregnancy testing (may be even monthly) to assist in providing evidence of efficacy for Cyclo-Provera. We would like to share with you the results of a recently concluded kinetic/dynamic study (M/5415/0006) that assessed 'return of ovulation based on serum progesterone ≥ 4.7 ng/mL' in 14 surgically sterile women who received three consecutive monthly injections of Cyclo-Provera. Kinetics and dynamics were assessed primarily post-third injection, though levels of E_2 , progesterone, and MPA were also measured at the end of the first and the second monthly injections.

Ovulation was confirmed in all women prior to study entry (control cycle). Complete suppression of serum progesterone by MPA is evident post-injection in all 14 women, which lasts throughout the monthly treatment period. The lack of luteal phase progesterone activity is clearly suggestive of complete inhibition of ovulation. Return of ovulation was seen over the range of 63-112 days post-last injection. These data strongly suggest that ovulation post-injection (within 33 days) should not be a concern with Cyclo-Provera I.M. injection. A complete final report is provided under Attachment 1.

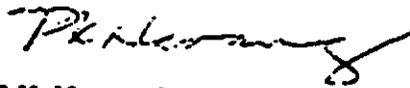
Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0189
USA

Telephone (616) 833-4000

Should you have any questions regarding this submission, please contact me at
(616) 833-9896. Please send any correspondence to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY



P.K. Narang, Ph.D., F.C.P.
Liaison Director

PKN/crdt

Attachments

cc: Ms. Christina Kish (+ FAX : 301 827 4267)

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

MEMORANDUM

Date: 8/11/98
To: Christina Kish
From: Ameeta Parekh (Acting Team Leader, OCPB)
Subject: Status of NDA 20-874

S

8/11/98

The original review of the NDA 20-874 was undertaken by Dr. Angelica Dorantes. Due to the limitations with the analytical methods, reliable pharmacokinetic information was not available from the data submitted in the NDA. Since a PK/PD study was ongoing at the time of this review, Office of Clinical Pharmacology and Biopharmaceutics deferred the final comments until the review of this information. It was also recommended that this information could be amended post-approval if the NDA were to be considered for approval based on safety and efficacy. Suggestions were provided for the package insert by Dr. Dorantes in her final review, in case of approval in absence of the above mentioned study.

Attached are the copies of recommendations from the original review. Also attached is a copy of the report on the body mass index data and the corresponding pharmacokinetic parameters (this was requested by the medical officer, but does not change the original recommendation from Dr. Dorantes).

CC: HFD-870 (Dorantes), HFD-580 (Kish)

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ON ORIGINAL



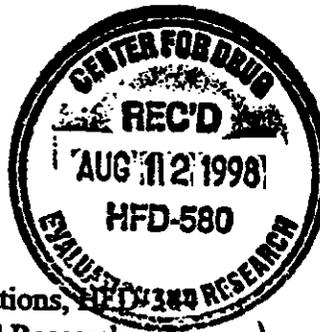
Pharmacia & Upjohn

ORIGINAL

Office of:
P.K. Narang, Ph.D., F.C.P.
Liaison Director, New Drugs
Regulatory Affairs

Telephone No. (616) 833-9896
Facsimile No. (616) 833-8237

August 7, 1998



ORIG AMENDMENT
151

Dr. Gurston Turner
Division of Scientific Investigations,
Center for Drug Evaluation and Research
Food and Drug Administration
7520 Standish Place
Rockville, MD 20855

151 noted

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS _____ DATE _____

RE.: NDA 20-874

Monthly Contraceptive

Request for Information

Dear Dr. Turner,

In preparation for your upcoming site audit to _____, we are providing a disk with an EXCEL spreadsheet for the patient information from that site per your request. This information was extracted from the data collected as part of the WHO Multicountry Study, Project 83913 (Protocol 001).

Hard copy documents are also attached which contain explanation of the EXCEL Data Structures (Attachment 1), Medical Event Listings (Attachment 2) and a directory listing for SAS data (Attachment 3).

- The Medical Events reported are based on the Complaint Question. The report lists the sequence of visits for which data exists for each patient and includes the complaint description when one was provided at a visit.
- The directory listing for the SAS data describes the data and some column descriptions that are found in the EXCEL spreadsheet. This was produced using the SAS data sets that were then downloaded to the EXCEL workbook.

The disk has been virus scanned using Dr. Solomon Anti-Virus Toolkit Version 7.84 and was noted to be virus-free.

Available information at Pharmacia & Upjohn suggests that the CPFs to 125/134 patients enrolled by the _____ site in _____ are at the site. Also, a translator (not a P&U employee) will be available to assist with the audit per your request.

Please let us know if any other information is needed to assist in your audit of this site by contacting P.K. Narang at (616) 833-9896. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY



P.K. Narang, Ph.D., F.C.P.
Regulatory Affairs

PKN:kmv

Attachments

cc: Christina Kish, Project Manager

APPEARS THIS WAY
ON ORIGINAL

Teleconference Meeting Minutes

Date: August 4, 1998 **Time:** 11:30 PM - 12:30 PM **Location:** Parklawn 17-43

NDA 20-874 **Drug Name:** _____ medroxyprogesterone acetate and estradiol
cypionate) Injection

External Participant: Pharmacia and Upjohn

Type of Meeting: review status discussion

Meeting Chair: Lisa Rarick, M.D.

External Participant Lead: Henk De Koning Gans

Meeting Recorder: Christina Kish

FDA Attendees:

Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products
(DRUDP;HFD-580)

Marianne Mann, M.D. - Deputy Director, DRUDP (HFD-580)

Susan Allen, M.D. - Medical Officer, DRUDP (HFD-580)

Julian Safran, M.D. - Medical Officer, DRUDP (HFD-580)

Christina Kish - Project Manager, DRUDP (HFD-580)

External Constituents:

Roger Garceau, M.D. - Clinical Development

Charlie Wajszczuk, M.D. - Clinical Development

Henk De Koning Gans, M.D. - Project Leader

P.K. Narang, Ph.D. - Director, New Drugs, Regulatory Affairs

Nancy Busso - Regulatory Affairs

Don Tong, Ph.D. - Biostatistics

Marie Maile, Ph.D. - Biostatistics

Matt Cromie - CTS

Diane Beuving - Project Manager

Meeting Objectives:

To discuss continuing review issues and concerns with the sponsor of this pending application.

Discussion Points:

- Safety Update
 - the safety update submitted July 16, 1998, addressed some of the safety and efficacy concerns discussed in the July 10, 1998 teleconference
 - the quality of the data presented in the safety update is also much improved from that of the original application

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August 4, 1998

- the safety update cannot adequately address the remaining concerns regarding the current application
- the proposed 6 month interim submission of data will not adequately address the remaining concerns regarding the current application
- U.S. clinical trial
 - the U.S. clinical trial will likely be considered the pivotal trial supporting this application for this drug product
 - sufficient data including 200 women completing 13 cycles for a year is required, but will not be obtained until close to study completion
 - the sponsor is strongly advised to ensure that sufficient women complete the required number of cycles with appropriate pregnancy testing
 - clinical information already submitted in this current application may be cited as supportive data

Decisions Reached

- an action will be taken by the September 26, 1998, goal date for this application
- the sponsor is strongly encouraged to complete the U.S. clinical trial before submitting further data from this trial
- the sponsor is advised to ensure that 200 women complete at least 13 cycles with appropriate pregnancy testing in the U.S. clinical trial
- although 10,000 women months of experience are normally required for a new hormonal contraceptive application, the sponsor may utilize the supporting clinical studies to address any deficit in cycles in the U.S. clinical trial
- the sponsor may submit a time table detailing when the required number of women/cycles are completed, when the U.S. study as a whole will be completed, and when the response to the action letter will be submitted in relation to the first two items

Unresolved Issues: none

Action Items:

<u>Item</u>	<u>person responsible</u>	<u>time frame</u>
determine user fee requirement for resubmission	C. Kish	7 working days
time table submission	sponsor	when available

CS

Minutes Preparer

8/12/98

CS

Concurrence, Chair

8/12/98

151

Internal Meeting Minutes

Date: July 30, 1998

Time: 4:30 PM - 5:00 PM

Location: Div. Dir. Office

NDA 20-874

Drug Name: _____ (medroxyprogesterone acetate and estradiol cypionate) Injection

Type of Meeting: status report

Meeting Chair: Lisa Rarick, M.D.

Meeting Recorder: Christina Kish

FDA Attendees:

Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP;HFD-580)

Marianne Mann, M.D. - Deputy Director, DRUDP (HFD-580)

Julian Safran, M.D. - Medical Officer, DRUDP (HFD-580)

Susan Allen, M.D. - Medical Officer, DRUDP (HFD-580)

Lana L. Pauls, M.P.H. - Chief, Project Management Staff, DRUDP (HFD-580)

Christina Kish - Project Manager, DRUDP (HFD-580)

Meeting Objectives:

To discuss the review status of this pending application.

Discussion Points:

- Clinical/Statistics
 - the Division contacted the sponsor on July 10, 1998, to express concerns with regard to the quality of the clinical data provided in the application; the sponsor was confident that these concerns would be addressed in the upcoming safety update
 - the sponsor expressed a willingness to provide interim data from the U.S. clinical trial to further address clinical concerns
 - the sponsor stated that the interim data would be prepared and submitted before the September goal date
 - the safety update for this application was received on July 17, 1998; it addressed some of the concerns relayed to the sponsor in the telecon of July 10, 1998
 - several major clinical issues remain unresolved (see attachment)
 - it is expected that upon completion of the U.S. clinical trial there may be sufficient information to support this application
 - the sponsor should ensure that a minimum of 200 women complete 13 cycles of _____ use with appropriate pregnancy testing
 - because pregnancy testing was not initiated until earlier this month, the sponsor may need to continue the U.S. clinical trial for a longer period of time to ensure that the minimum required number of women/cycles are completed with this study
 - interim U.S. clinical data will not provide sufficient information to allow approval of the current application

July 30, 1998

Decisions Reached:

- a teleconference with the sponsor should be scheduled for the week of August 3, 1998, to inform them that the review of the application and the safety update is insufficient to support approval
- the sponsor should be informed that further interim data from the ongoing U.S. trial will probably not provide sufficient information to support the approval of the current application
- the sponsor should be advised to ensure the minimum required women/cycles are completed in the U.S. clinical trial to provide sufficient information for an adequate response to the clinical deficiencies
- ideally, the sponsor should complete the U.S. clinical trial and then submit this information as an NDA resubmission

Unresolved Issues: none

Action Items:

<u>Item</u>	<u>person responsible</u>	<u>time frame</u>
schedule a teleconference	C. Kish	7 working days
<i>S</i>		
Minutes Preparer	<i>8/11/98</i>	<i>8/11/98</i>
		Concurrence, Chair

ATTACHMENT

cc:

Orig. IND
HFD-580

MEETING ATTENDEES

HFD-580/JMeroier/LPauls

HFD-580/CKish/7.30.98/n20874.st2

Concurrence: Mmann 8.6.98/LRarick 8.6.98/LPauls 8.3.98/SAllen 8.3.98/JSaffran 8.4.98

MEETING MINUTES

**APPEARS THIS WAY
ON ORIGINAL**

Issues Addressed and Still Remaining for Cyclo-Provera as of July 30, 1998

Issues Addressed by Safety Update

1. Data quality

- a. Ethnic diversity of study population appears to be addressed
- b. CRFs and source documents will be available for review and audit
- c. Comprehensive information on specific safety issues (Hb, HCT, lipids, coagulation factors, carbohydrate metabolism) is being collected at appropriate intervals.
- d. CRFs are designed to collect information on pregnancy testing and on use of concomitant medications

2. Efficacy issues

- a. Pregnancy testing on a monthly basis and at discontinuation was instituted as of July 22, 1998

3. Safety issues

- a. Administration of hormonal compounds during the trial for any reason results in discontinuation from the study.
- b. Per the sponsor, treatment of bleeding disturbances with products other than iron therapy is not permitted, although this is not specifically stated in the protocol.
- c. Other safety parameters are being monitored as described in 1(c)

Issues Not Adequately Addressed by Information in the Safety Update

1. Data quality

a. Sample size

- i. Update is based on limited drug exposure experience in 782 women initially enrolled in the Cyclo-Provera arm of the study
 - ii. 25.3% (n = 198) of those enrolled have discontinued treatment, leaving 584 women still enrolled as of 3/31/98
 - iii. Average # weeks of exposure as of 3/31/98 = 26.5 weeks (out of a planned 60 weeks total exposure)
 - iv. No patients completed one year of Cyclo-Provera use as of 3/31/98
- b. CRFs included in the Update are only those for women who discontinued due to adverse events (n = 122), not for all women currently enrolled.
 - c. Tremendous variability in discontinuation rates across study sites (0%-62%)

2. Efficacy issues

- a. The total number of patients who will complete or discontinue the study *having had appropriate pregnancy testing performed* is unknown and may not provide enough women-months of exposure to demonstrate efficacy.
- b. Several of the inclusion criteria are virtually identical to those in the pivotal trials and may have resulted in enrollment of women not at risk of pregnancy at study entry.
- c. The use of EC is not addressed in the protocol or its amendments

3. Safety issues

- a. No information is provided on what, if any, treatments are being given for bleeding disturbances
- b. No information is provided in the Update on bleeding patterns and pattern changes with Cyclo-Provera use, despite the fact that this is the primary study endpoint.
- c. Although some data is available yet on effects of Cyclo-Provera on lipid parameters, serum chemistry and carbohydrate metabolism, the sample sizes are too small to draw conclusions about these effects over time.

Conclusions

Although the information contained in the Safety Update does address many of our concerns regarding data quality and provides some safety data related to Cyclo-Provera use, the information is based upon limited product exposure in a subset of the study population.

We believe it is important to have data from the completed US trial before proof of safety or efficacy can be demonstrated. In particular, we would like to see safety and efficacy information for women who have used the product for 13 cycles. No information was available in the Safety Update on patients who had completed one-year of Cyclo-Provera use.

APPEARS THIS WAY
ON ORIGINAL

Questions

1. If there were 582 women still enrolled as of 3/31/98, what is the minimum # of participants that must complete 13 cycles of Cyclo-Provera use in order to demonstrate efficacy, and do we think this number is achievable?

2. Could we accept demonstration of efficacy in either 200 women who complete 13 cycles of product use or 10,000 woman-months of exposure?
 - a. If we are going to require that at least 200 women complete 13 cycles of use with a minimum of 10,000 cycles, we should inform P&U that Cyclo-Provera will be held to this standard. They could extend subject participation (duration of exposure) accordingly if they see that these requirements are not going to be met at the conclusion of the ongoing US study.

3. If they are not going to meet the requirements in #2, should we advise them to increase their enrollment of study participants and, if so, to what number?
 - a. NOTE: 47% of women enrolled in the US study are OC users who were not required to go through a wash-out period prior to Cyclo-Provera use, and (as in the pivotal trials) were not necessarily at risk of pregnancy at study enrollment. Is there any way for us to analyze data from these subjects that would provide meaningful efficacy rates?

200 ♀ 13 cycle = minimum

Dec 11 - 10:00
Jan 11 - 10:00
Mon 1/11 at 10:00

APPEARS THE
ON ORIGINAL



Pharmacia & Upjohn

NEW CORRESP

ORIGINAL

P.K. Narang, Ph.D., F.C.P.
Liaison Director, New Drugs
Regulatory Affairs
Telephone No. (616) 833 9896
Facsimile No. (616) 833 0409

July 28, 1998

Lisa Rarick, M.D.
Division of Reproductive and Urological Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

REVIEWS COMPLETED

CSO ACTION:

LETTER N.A.I. MEMO

CSO INITIALS

DAT

RE: NDA 20-874

**Monthly Contraceptive
(Medroxyprogesterone Acetate and
Estradiol Cypionate Injection)**

General Correspondence

Dear Dr. Rarick

On June 29, 1998, P&U submitted responses to questions identified during the June 5, 1998 telecon following review of the ISS/ISE for the NDA for Cyclo-Provera. For the questions (Nos. 7, 10, 15) remaining unanswered, we expected to provide a response at the time of the Safety Update (submitted July 16, 1998), but some concentration-time data from Phase I trials were still under analysis.

Appended please find the responses to the three remaining questions from the Medical and Pharmacokinetic reviewer. We hope that this new information relating time to return of ovulation to select kinetic estimates (data from study Protocol /0006) along with BMI effect on drug levels (study Protocol /0004) will assist the Division in its ongoing assessment of the safety/efficacy of Cyclo-Provera. We anticipate finalizing the report for study Protocol M/5415/0006 in a week.

For any questions regarding the contents of this submission, please contact P.K. Narang (616 833 9896). Please send correspondence addressed to unit 0635-298-113.

Sincerely

P.K. Narang, Ph.D., F.C.P.
Liaison Director
Regulatory Affairs

cc: Christina Kish, Project Manager (letter only)





Pharmacia & Upjohn

Office of:
P.K. Narang, Ph.D., F.C.P.
Liaison Director, New Drugs
Regulatory Affairs

Telephone No. (616) 833-9896
Facsimile No. (616) 833-8237

July 16, 1998

Dr. Lisa Rarick
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-874
——— Monthly
Contraceptive (Medroxyprogesterone
Acetate and Estradiol Cypionate
Injection)

SAFETY UPDATE

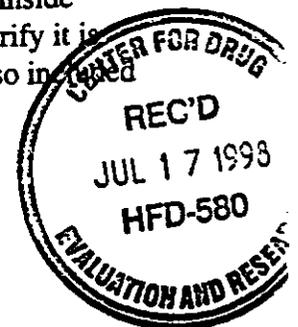
Dear Dr. Rarick:

In accordance with 21 CFR § 314.50(d)(5)(vi)(b)(1), Pharmacia and Upjohn is submitting a Safety Update Report for ——— Monthly Contraceptive (medroxyprogesterone acetate and estradiol cypionate injection) which provides substantial new information pertinent to the assessment of its safety, e.g., 'Laboratory Evaluations' (Hematology, Chemistry and Urinalysis), Lipids and Adverse Events by 'Race'. This information is from the ongoing US Phase III study (M/5415/0004). The data cut-off date for the purposes of this Safety Update Report was March 31, 1998.

Appendix 6 which involves the associated case report forms for deaths (none) and drop-outs due to adverse events has been provided only in electronic format (pdf files) per previous discussions with Ms. C. Kish (Project Manager). The CD-ROM is located in the inside cover. The disk has been scanned with McAfee Virus Scan software (3.1.1) to verify it is free of viruses. A copy of this letter, Form 356h and the Table of Contents are also included.

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA

Telephone (616) 833-4000



on the disk. A listing of the patient numbers have been bookmarked to the individual case report forms. The patient records can be sorted by "domain" profiles or by sequential "visits". Please note that the case report form records were stored electronically a few months after the report cut-off date of March 31, 1998. Therefore records may appear on this electronic version which were not available at the time of data assessments for the actual Safety Update Report and which have not been included in the Safety Update Report.

If you have any questions regarding this submission, please contact me at (616) 833-9896. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY



P.K. Narang, Ph.D., F.C.P.
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL



Pharmacia & Upjohn

ORIGINAL

NEW CORRESP

noted
15/2/98

Office of:
P.K. Narang, Ph.D., F.C.P.
Liaison Director, New Drugs
Regulatory Affairs

Telephone No. (616) 833-9896
Facsimile No. (616) 833-8237

151 7/22/98
151 7/27/98

July 15, 1998

Dr. Lisa Rarick
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

REVIEWS COMPLETED	
CSO INITIALS	DATE
<input type="checkbox"/>	7/24/98
CSO INITIALS	DATE

RE: NDA 20-874

Monthly Contraceptive
(Medroxyprogesterone Acetate and
Estradiol Cypionate Injection)

General Correspondence

Dear Dr. Rarick:

During a recent review of Safety Update information, it was noted that the tables provided with our previous response letter dated June 29, 1998, regarding weight gain contained incorrect data. The corrected tables have been enclosed and should replace the tables in Attachment 5 of the June 29th packet. The text for Response Numbers 13 and 18 which referred to that data have also been revised accordingly. Revised pages have been enclosed and should replace the previous pages.

Also, P&U correspondence dated June 30 in response to the teleconference of June 19 mentioned that we were still trying to clarify the therapeutic class for the treatment drug "Sedatrium". This drug was noted to have been used for treatment of a patient who experienced angina. Information has been received by our medical colleagues in _____ that this drug name is actually "Sedativum" which is used in _____ as a collective name for sedative drugs.

If you have any questions regarding the replacement pages, please contact P.K. Narang (616-833-9896). Please send correspondence addressed to Unit 0635-298-113.

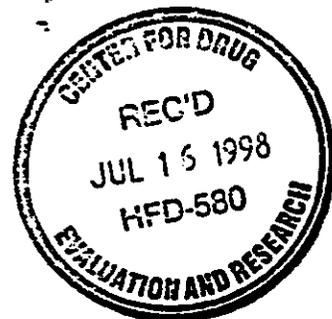
Sincerely,

PHARMACIA & UPJOHN COMPANY

P.K. Narang, Ph.D., F.C.P.
Liaison Director
Regulatory Affairs

NJB/crdt:Attachments
cc: Ms. Cristina Kish (Project Manager)

Pharmacia & Upjohn Telephone (616) 833-4000
7000 Portage Road
Kalamazoo, MI 49001-0199
USA



BEST POSSIBLE COPY

Teleconference Meeting Minutes**Date:** July 10, 1998**Time:** 1:00 PM - 1:30 PM**Location:** Parklawn 17-43**NDA** 20-874**Drug Name:** — (medroxyprogesterone acetate and estradiol cypionate) Injection**External Participant:** Pharmacia and Upjohn**Type of Meeting:** information request discussion**Meeting Chair:** Lisa Rarick, M.D.**External Participant Lead:** Henk De Koning Gans**Meeting Recorder:** Christina Kish**FDA Attendees:**

Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP;HFD-580)

Marianne Mann, M.D. - Deputy Director, DRUDP (HFD-580)

Susan Allen, M.D. - Medical Officer, DRUDP (HFD-580)

Julian Safran, M.D. - Medical Officer, DRUDP (HFD-580)

Lana L. Pauls, M.P.H. - Chief, Project Management Staff, DRUDP (HFD-580)

Christina Kish - Project Manager, DRUDP (HFD-580)

External Constituents:

Roger Garceau, M.D. - Clinical Development

Charlie Wajszczuk, M.D. - Clinical Development

Henk De Koning Gans - Project Leader

P.K. Narang, Ph.D. - Director, New Drugs, Regulatory Affairs

Nancy Busso - Regulatory Affairs

Kathy Derr - Medical Writer

Matt Cromie - CTS

Meeting Objectives:

To discuss review issues and concerns with the sponsor of this pending application.

Discussion Points:

- **Background**
 - the application provides for a monthly injectable contraceptive
 - the pivotal studies were carried out several years ago by WHO
 - most of the case report forms are missing for the study sites

July 10, 1998

- most of the sites are not auditable with regard to clinical data
- protocols were not strictly adhered to by study sites
- a U.S. supportive clinical trial is currently underway and is expected to be completed first quarter next year
- a safety update containing preliminary results of the U.S. clinical trial will be submitted before the end of the month
- the table of contents for the safety update has been submitted prior to this teleconference

- **Review Issues**

- problems with regard to safety and efficacy of this application include the following:
 - only 8% of the study sites are auditable
 - study sites vary in the quality of the data available
 - when recorded, there was capacity to record only two adverse events for each patient
 - it appears that women who may not have been fertile (i.e., due to recent abortion or recent/possibly current use of contraceptives) were enrolled in the studies
 - pregnancy tests were only performed when "deemed necessary" this term has not been clearly defined nor does it appear to have been consistent between centers
 - uncontrolled or unusual bleeding was treated differently at different sites, treatments included, amongst other things, use of hormones
 - bleeding rates and frequency of anemia cannot be verified in the pivotal trials due to a lack of Hg and HCT testing throughout the pivotal trials

- **U.S. Study**

- information from the U.S. clinical trial will be submitted in the safety update
- the U.S. study was initiated to support the pivotal trials with data from the targeted market population
- the sponsor asserts that both drugs in the application are well known and characterized, a positive outcome is expected for the U.S. study
- the sponsor further stated that the safety update should adequately address safety concerns and questions regarding bleeding patterns, these data could be expected to accurately reflect data missing from the original pivotal trials
- the U.S. clinical trial treats prolonged bleeding by iron supplements (if anemia occurs) after which, depending on response to treatment, the subject may or may not be discontinued from the study

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July 10, 1998

- pregnancy testing has been performed at baseline and then when necessary, however women who discontinue are not automatically given a pregnancy test nor are those who complete the study protocol. Monthly pregnancy testing is not being performed
- follow-up pregnancy testing is not planned at this time
- the U.S. clinical trial will be completed in February 1999
- the sponsor is urged to perform pregnancy tests on every subject left in the clinical trial every month until the subject has completed the trial or has withdrawn from the trial
- additionally, subjects who complete or withdraw from the clinical trial should be given an exit pregnancy test

Decisions Reached

- the application does not contain adequate information on which to base a positive decision
- the _____ site will be audited and depending on results, an inspection of the site in _____ may be carried out
- the sponsor will submit the safety update before the end of the month
- a second teleconference may be held after review of the safety update
- the sponsor will begin to collect six month interim data from the U.S. clinical trial to be submitted before completion of the review cycle. The sponsor expects that this additional data will allay some of the concerns expressed in this teleconference with regard to safety and efficacy of this drug product

Unresolved Issues: none

Action Items: see decisions reached

Minutes Preparer

7/21/98

Concurrence, Chair

7/31/98

Post-meeting note: The sponsor contacted the Division on July 22, 1998, to state that pregnancy testing will be carried out monthly. The sponsor asked if urine testing would be acceptable and whether the utilization of the same test kit at each site would be acceptable for standardization of the results. The sponsor was told that these two proposals were acceptable. The sponsor expects to submit six month interim data the first week of September.

APPEARS TRUE
ON ORIGINAL

NDA 20-874

Page 4

July 10, 1998

cc:

Orig. NDA

HFD-580

MEETING ATTENDEES

HFD-580/LPauls/JMercier

HFD-580/CKish/7.22.98/n20874.tc

concurrence:JSafran 7.27.98/SAllen 7.27.98/MMann 7.23.98/LRarick 7.31.98

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

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Meeting Minutes

Date: July 1, 1998 **Time:** 9:30 AM - 10:00 AM **Location:** Parklawn 17-43

NDA 20-874 **Drug Name:** Cyclo-Provera (medroxyprogesterone acetate and estradiol cypionate) Injection

Type of Meeting: 10 month status report

Meeting Chair: Lisa Rarick, M.D.

Meeting Recorder: Christina Kish

FDA Attendees:

Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP;HFD-580)

Marianne Mann, M.D. - Deputy Director, DRUDP (HFD-580)

Susan Allen, M.D. - Medical Officer, DRUDP (HFD-580)

David Lin, Ph.D. - Chemist, DNDCII @ DRUDP (HFD-580)

Angelica Dorantes, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Christina Kish - Project Manager, DRUDP (HFD-580)

Meeting Objectives:

To discuss the review status of this pending application.

Discussion Points:

- Clinical/Statistics
 - the requested statistical information has been received and will be reviewed
 - clinical review is ongoing and there is concern regarding the database quality
 - although _____ was originally requested as a clinical audit site, the sponsor has indicated that there are no source documents to audit, therefore the request to DSI to audit this site should be withdrawn
 - an additional clinical site in _____ should be audited as requested in a recent memo to DSI, depending on the information obtained at this site, an additional site in the _____ may be requested
 - at this time the review team is recommending non-approval based on inadequate clinical trial data
 - the sponsor is currently conducting a U.S. clinical trial which may provide sufficient information to support an NDA once it is completed
 - the sponsor expects that the U.S. trial would be available for submission in June, 1999

July 1, 1998

- CMC
 - the original review of this application was completed and an information request letter sent to the sponsor on April 30, 1998
 - the sponsor has submitted a complete response which appears adequate
 - additionally the sponsor was notified March 4, 1998, that their proposed tradename was unacceptable
 - the sponsor has submitted the tradename _____ for consideration
 - the Labeling and Nomenclature Committee has been requested to review this proposal at their next meeting to be held in July
 - the reviewing chemist expects to complete the review of this application by next week and expects to recommend approval

- Clinical Pharmacology
 - the Clinical Pharmacologist has completed the review of this application
 - a letter recommending revisions to the Clinical Pharmacology section of the proposed labeling is currently circulating and is expected to be sent to the sponsor next week
 - a PK/PD study report is expected to be submitted by the end of July and will be reviewed as part of this application
 - because the user fee goal date for this application is September 26, 1998, the expected PK/PD submission may extend the goal date for the application

Decisions Reached:

- a teleconference with the sponsor should be scheduled next week to inform them that the review of the application does not support approval due to the lack of auditable clinical data
- the sponsor should be informed that data from the ongoing U.S. trial may provide auditable clinical data, and may therefore support their NDA; this data may be available in June, 1999 according to the sponsor
- the sponsor should be informed that submission of the PK/PD study may extend the User Fee goal date, however, if they decide to withdraw their application this may not be relevant
- a clinical audit of the _____ site clinical data will be conducted; DSI should be contacted in this regard
- following the teleconference with the sponsor, additional action (non-approval) will be taken if necessary

Unresolved Issues: none

July 1, 1998

Action Items:

Item	person responsible	time frame
1. schedule a teleconference	C. Kish	7 working days
2. contact DSI regarding site audit	C. Kish	7 working days

|S|

|S|

Minutes Preparer

7/22/98

Concurrence, Chair

7/22/98

Post-meeting note: a teleconference has been scheduled with the sponsor for July 10, 1998. It was recently decided by Dr. Lumpkin that the Divisions may not give sponsors the option to withdraw an application before issuing a not approval action, however the Division may discuss how a review is progressing and the sponsor may choose to initiate withdrawal based on that discussion.

DSI was contacted and an e-mail sent with the required clinical audit revisions July 2, 1998. DSI confirmed receipt of the e-mail the same day.

cc:

Orig. IND

HFD-580

MEETING ATTENDEES

HFD-580/JMercier/LPauls

HFD-580/CKish/7.22.98/n20874.stm

Concurrence:LRarick 7.13.98/ADorantes 7.2.98/DLin 7.6.98/SAllen 7.7.98/MMann 7.7.98

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL



Pharmacia & Upjohn

P.K. Narang, Ph.D., F.C.P.
Liaison Director, New Drugs
Regulatory Affairs
Telephone No. (616) 833 9896
Facsimile No. (616) 833 0409

June 30, 1998

T.S.I.
7/7/98
ORIG AMENDMENT

Lisa Rarick, M.D.
Division of Reproductive and Urological Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 20-374
Monthly Contraceptive
(Medroxyprogesterone Acetate and
Estradiol Cypionate Injection)

General Correspondence

Dear Dr. Rarick,

Appended please find responses to questions from June 19, 1998 teleconference between Division's Medical Reviewers and P&U, along with a list of the participants from Pharmacia and Upjohn.

Should you have any questions, please contact me. Please send any correspondence to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

P.K. Narang, Ph.D., F.C.P.
Liaison Director
Regulatory Affairs

PKN:SEH
Enclosures

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

cc: Ms. Christina Kish (Project Manager) - Letter Only

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA

Telephone (616) 833-4000

BEST POSSIBLE COPY



Pharmacia & Upjohn

P.K. Narang, Ph.D., F.C.P.
Liaison Director, New Drugs
Regulatory Affairs
Telephone No. (616) 833 9896
Facsimile No. (616) 833 0409

June 29, 1998

Lisa Rarick, M.D.
Division of Reproductive and Urological Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-874

Monthly Contraceptive
(Medroxyprogesterone Acetate and
Estradiol Cypionate Injection)

General Correspondence

Dear Dr. Rarick:

Please submit the tradename/proprietary name _____ to the Labeling and Nomenclature Committee for review. This would replace Cyclo-Provera submitted previously but deemed inappropriate by the agency. Pharmacia and Upjohn would appreciate a prompt review, preferably at the next upcoming committee meeting.

If you have any questions regarding this submission, please contact me at (616) 833-8527. Please send any correspondence to Unit 0635-298-113.

Sincerely,

P.K. Narang, Ph.D., F.C.P.
Liaison Director

cc: Ms. Christina Kish (FAX this letter to 301 827 4267) + Letter Only

ORIGINAL



Pharmacia & Upjohn

Office of:
P.K. Narang, Ph.D., F.C.P.
Liaison Director, New Drugs
Regulatory Affairs

Telephone No. (616) 833-9896
Facsimile No. (616) 833-8237

June 29, 1998

TS1
ORIG AMENDMENT

The tradename
has been submitted
to the LNC (6/30/98)
(15)
7/13/98



Lisa D. Rarick, M.D.
Division of Reproductive and Urological Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

IS1 7/13/98
IS1 7/22/98

RE: NDA 20-874
Monthly Contraceptive
(Medroxyprogesterone Acetate and
Estradiol Cypionate Injection)

General Correspondence

Dear Dr. Rarick:

Pursuant to the tele-conversation of June 5, 1998, appended please find the responses to specific questions from the review of the ISS and ISE of the above mentioned NDA. Under separate cover, we are submitting the tradename/proprietary name _____ to the Labeling and Nomenclature Committee for review and this would replace Cyclo-Provera previously deemed inappropriate.

If you have any questions regarding the contents of this submission, please contact P.K. Narang (616) 833-9896. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

P.K. Narang, Ph.D., F.C.P.
Regulatory Affairs

PKN:law:Attachments

cc: Christina Kish, Project Manager (letter only)

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> N.A. <input type="checkbox"/> MEMO
CSO INITIALS _____ DATE _____



Pharmacia & Upjohn

ORIGINAL

NEW CORRESP

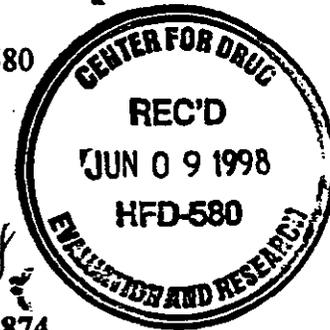
Office of:
Nancy J. P...so, R.Ph.
Regulatory Manager
U.S. Regulatory Affairs

Telephone No. (616) 833-8554
Facsimile No. (616) 833-8237

June 5, 1998

Division of Reproductive & Urological Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

NGT
151 6/12/98



RE: NDA 20-874
CYCLO-PROVERA® Contraceptive
Injection (Medroxyprogesterone
Acetate and Estradiol Cypionate)

General Correspondence

Dear Ms. Kish,

Based on our phone conversation of May 26, we are providing the following documents and/or disks to assist in the review process:

- Disk labeled "CycloProvera SAS Data"**
This disk contains the SAS datasets for the clinical data including Multicountry Study (M/5415/0001), Egypt Study (M/5415/0002) and China Study (M/5415/0003).

The disk also contains a "readme" file which explains the disk content and the process to unzip the SAS transport data, a document to describe the data structure of the SAS data library, a file to cover the data from transport format to SAS data library, a code file to link the format catalogs for data and a copy of the "Notes to Reviewer" which was included with the NDA submission. (The "Notes to Reviewer" describes the rules applied to raw data to create the SAS data library from which the ISS tables were produced.)

Hard copies of the text files (i.e., not including the actual data) can be found in Attachment 1.

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS _____ DATE _____

2. **Disk labeled "Integrated Summary of Safety" for Cyclo-Provera**
This disk contains the electronic version of the Integrated Summary of Safety as a '.pdf' document.
3. **Disk labeled "Labeling - Electronic Version" for Cyclo-Provera**
This disk contains the labeling for Cyclo-Provera as submitted in the NDA.

The Non-Insert (carton and label) file is a WORD document (nonpilab.doc)

The package insert is a ".pdf" documents (cyclopi.pdf)

The patient package insert is a WORD document (cycloppi.man)

4. **Clinical Trial Site Audit Information: Provided by Clinical Quality Assurance (Attachment 2)**

WHO PROJECT No. 83913 : MULTICOUNTRY STUDY (Protocol M/5415/0001)

As you are aware, WHO (World Health Organization) conducted this study between 1984 and 1987, prior to most international GCP guidelines. To assess the availability or adequacy of records, P&U Clinical Quality Assurance (CQA) unit undertook a review of several investigational sites. The results of this recently completed endeavor are tabulated in Attachment 2. As would be expected, some centers, for various reasons, no longer have records available for review. The Case Report Forms (CRFs) for this study were obtained by WHO and retained in their files until their transfer to P&U, where they are now retained. Some other study records were apparently not routinely obtained/stored by WHO. The attached table reflects the efforts made to contact various sites, the results of such contacts and visits made to sites with reported availability of some records. (Documentation of contacts/attempted contacts with these sites is available at P&U CQA).

OTHER PERTINENT SITE-SPECIFIC INFORMATION

1. Recently (May 20, 1998), the Division of Scientific Investigations (Clinical Investigations Branch) requested arrangements to visit three sites (_____ and _____, in _____). As can be seen from Attachment 2, audits show that two of the sites (_____ and _____, selected for inspection no longer have any records. We would like to share this information with you to assist in the selection process of alternative centers, if needed.

_____, the investigator of record at the _____ site, will not be available during the first three weeks in August. She would be available Sept 1 - 4. Further, _____, the overall coordinator for all the sites in _____, has indicated availability during the week of Sept 7 to 11th.

NDA 20-874

Page 3

If you have any questions regarding this submission, please contact Nancy J. Busso at (616) 833-8554. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Nancy J. Busso, R.Ph.

Nancy J. Busso, R.Ph.
Regulatory Manager
Regulatory Affairs

NJB:law

Attachments

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY



Pharmacia & Upjohn

Office of:
Donald R. Giesecker, Pharm.D.
Associate Director
Regulatory Affairs

Telephone No. (616) 833-8527
Facsimile No. (616) 833-8237

May 21, 1998

Lisa D. Rarick, M.D.
Division of Reproductive & Urological Drug Products HFD-580
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-874
CYCLO-PROVERA® Contraceptive Injection
(Medroxyprogesterone Acetate and
Estradiol Cypionate)

General Correspondence

Dear Dr. Rarick,

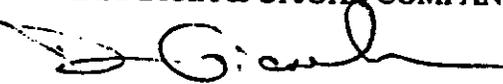
The following pages include responses to your letter of April 30, 1998.

Please note that a new tradename (Comment 7) is being finalized internally and should be submitted for review soon. The labeling suggestions (Comment 8) will be implemented as stated. However, we plan to incorporate those changes with any additional labeling suggestions resulting from the remaining review process and propose to submit revised labeling, including the current suggestions at that time.

If you have any questions regarding the contents of this submission, please contact Donald R. Giesecker at (616) 833-8527. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY


Donald R. Giesecker, Associate Director
Regulatory Affairs

DRG:kmv
Attachments

cc: Christina Kish (Project Manager) - Letter only

APPEARS THIS WAY
ON ORIGINAL

/S/

Pharmacia and Upjohn
Attention: Mr. Don Geisiker
Regulatory Manager, U.S. Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 49001

APR 30 1998

Dear Mr. Geisiker:

Please refer to your pending September 25, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for medroxyprogesterone acetate and estradiol cypionate for injection.

We have completed our review of the Chemistry Manufacturing and Controls section of your submission and have identified the following deficiencies:

1. Please indicate whether you plan to perform any reprocessing operations on the drug product if it does not meet release specifications.
2. There is a discrepancy between the relative response factors submitted for the _____ MPA analog in the HPLC assay _____. The table on page 1.4:4/1/101 reports this value to be _____ relative to MPA, however on the table on page 1.4:4/1/145 a value of _____ is given. Please clarify this discrepancy.
3. The pH specification you propose for the drug product of _____ at expiry is different from the pH range approved for other sterile medroxyprogesterone acetate suspensions, which is 3.0-7.0. This latter range is also provided for in the USP monograph for Sterile Medroxyprogesterone Acetate Suspension. Your pH range for this drug product should be revised to 3.0-7.0.
4. The proposed post-approval stability storage conditions, _____ do not match the conditions used to generate the primary stability data, _____. The post-approval stability conditions should be _____.
5. The pH of the drug product decreases over time in the stability studies. Please comment on a possible mechanism for this observation.
6. The assay values of the drug substances at time _____ in the stability study were _____ and _____ for medroxyprogesterone acetate and _____, and _____ for estradiol cypionate. This would seem to indicate the use of manufacturing _____ for both of the drug substances. The proposed batch formula submitted for the drug product does not call for _____, yet significant _____ are present for both drugs in the stability batches submitted. The use of a manufacturing _____ unless justified by data demonstrating _____ during the manufacturing process is unacceptable. Please clarify this issue.

7. As stated in our correspondence of March 4, 1998, your proposed tradename of _____ is unacceptable. A new tradename should be submitted for review.
8. The description section of the package insert refers to the drug product as " _____ ." this should be changed to read, _____
_____ In addition the statement, _____
_____ should be added.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Christina Kish, Project Manager, at (301) 827-4260.

Sincerely,

[]

4/20/98

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

Orig. NDA
HFD-580
HFD-580/MRhee/RSeevers/MMann
HFD-820/ONDC Division Director
HFD-580/CKish/4.24.98/n20874.irc
concurrence:MRhee 4.27.98/MMann 4.27.98/LRarick 4.27.98

INFORMATION REQUEST (IR)

APPEARS THIS WAY
ON ORIGINAL

151

NDA 20-874

MAR 4 1998

Pharmacia & Upjohn
Attention: Mr. Don Geisiker
Regulatory Manager, U.S. Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 49001

Dear Mr. Geisiker:

Please refer to your pending September 25, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cyclo-Provera Contraceptive Injection.

We have completed our review of your proposed tradename "Cyclo-Provera" and find it unacceptable for the following reason:

Under 21 CFR 201.6(b), "the labeling of a drug which contains two or more ingredients may be misleading . . . by the designation of such drug in labeling by a name which includes or suggests the name of one or more but not all ingredients, even though the names of all such ingredients are stated elsewhere in the labeling." Therefore, the name "Cyclo-Provera" is not acceptable because while the _____ component is identified, the estradiol component is not.

Please propose an alternate tradename so that it can be forwarded to the Labeling and Nomenclature Committee for review.

If you have any questions, please contact Ms. Christina Kish at (301) 827-4260.

Sincerely,



3/5/98

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Office Of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

Orig. NDA
HFD-580
HFD-580/RSeevers/MRhee/LRarick/SSlaughter/deputy director
HFD-580/CKish/2.25.98/n20874.gc
concurrence:RSeevers 2.25.98/MRhee 2.25.98/LRarick 3.2.98

GENERAL CORRESPONDENCE

6 Month Status Meeting

Date: March 2, 1998 **Time:** 9:00 AM - 9:30 AM **Location:** Parklawn 17B-43

NDA: 20-874 **Drug Name:** Cyclo-Provera (medroxyprogesterone acetate and ethinyl estradiol) injection

Meeting Chair: Christina Kish

Meeting Recorder: Christina Kish

Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products
(DRUDP;HFD-580)

Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Paul Stinavage, Ph.D. - Molecular Biologist, Office of New Drug Chemistry (ONDC) @ (HFD-160)

Christina Kish - Project Manager, DRUDP (HFD-580)

Discussion Points:

- **Clinical**
 - the medical officer is currently on maternity leave
 - the medical officer is aware of the due date for this application and is expected to have it completed on time
- **Chemistry, Manufacturing and Controls (CMC)**
 - all EER's are complete and acceptable
 - the review is expected to be completed June
 - to date no major deficiencies have been identified
 - the sponsor was sent a letter dated March 4, 1998, stating that their proposed tradename is unacceptable because only one of the two active ingredients is identified in the name
- **Biopharmaceutics**
 - will initiate review in May
- **Statistics**
 - the application has been consulted out to Dr. Girish Aras in HFD-715
- **Toxicology**
 - the review is complete and is recommended for approval

- Microbiology
 - review is expected to be completed by March 15, 1998
 - no deficiencies have been identified
 - will recommend approval of the application

Action Items:

1. The statistician, Dr. Aras, should be contacted regarding the status of his review and his projected completion date.
2. The medical officer, Dr. Golden should be contacted on her return to assess the status of the review and her projected completion date.

/S/

/S/

Minutes Preparer

3/12/98

Concurrence, Chair

3/12/98

cc:

Orig. IND

HFD-580

MEETING ATTENDEES

HFD-580/JMercier/LPauls

HFD-713/GAras

HFD-580/CKish/3.2.98/n20874.6mo

concurrence: PStinavage 3.5.98/LPauls 3.5.98/LRarick 3.6.98/LKammerman 3.10.98

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL



DUPLICATE
Pharmacia & Upjohn

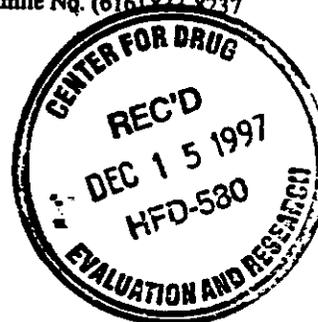
Office of:
James H. Chambers
Regulatory Manager
U.S. Regulatory Affairs

Telephone No. (616) 833-1397
Facsimile No. (616) 833-8237

December 12, 1997

151
ORIG AMENDMENT

Lisa D. Rarick, M.D.
Division of Reproductive & Urological Drug Products HFD-580
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 20-874

Contraceptive Injection
(Medroxyprogesterone Acetate and
Estradiol Cypionate)

AMENDMENT #2

Dear Dr. Rarick,

On November 18, 1997, a teleconference was held to discuss additional analyses for NDA 20-874 CYCLO-PROVERA Contraceptive Injection. This teleconference was held at the request of the Division to address subpopulation analyses based on race. Participating in this teleconference were Ms. Christina Kish and Dr. Lisa Kammerman from FDA and Donald Tong, Henk deKoningGans and James Chambers from Pharmacia & Upjohn. During the course of this teleconference, Pharmacia & Upjohn indicated that it does not have individual patient race designation for the three pivotal studies. The demographic breakdown by race found in the NDA is based on an assumption of racial homogeneity by country.

Additionally, it was pointed out that there were no pregnancies in the Multicountry study and only 5 total in the Egypt and China studies. Dr. Kammerman requested that we provide a discussion of the race assumptions that were made during the analyses. This discussion is provided as Enclosure #1. This discussion also includes a table of race breakdown for supportive studies as reported in the literature.

If you have any questions regarding the contents of this submission, please contact James H. Chambers at (616) 833-1397. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

James H. Chambers, Regulatory Manager
U.S. Regulatory Affairs

JHC:law

**APPEARS THIS WAY
ON ORIGINAL**



ORIGINAL Pharmacia & Upjohn

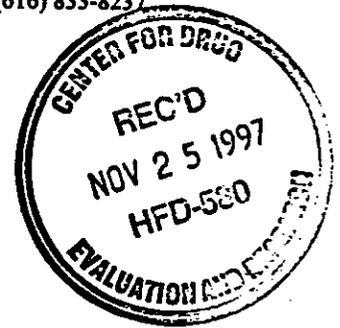
Office of:
James H. Chambers
Regulatory Manager
U.S. Regulatory Affairs

Telephone No. (616) 833-1397
Facsimile No. (616) 833-8237

NEW CORRESP

November 24, 1997

Lisa D. Rarick, M.D.
Division of Reproductive & Urological Drug Products HFD-580
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 20-874
CYCLO-PROVERA® Contraceptive Injection
(Medroxyprogesterone Acetate and
Estradiol Cypionate)

AMENDMENT #1

Dear Dr. Rarick,

Following discussions with Ms. Lana Pauls and Ms. Christina Kish of your division regarding difficulties in locating crucial items, we are providing revised Items 8 and 10 (Clinical and Statistical) for NDA 20-874 CYCLO-PROVERA Contraceptive Injection. The sixty-four (64) volumes included in this submission, 1.1, 1.2, 1.3, 1.12 and 1.15 - 1.74, supercede those previously submitted in the original submission on September 25, 1997.

In this revised Item 8 and 10, the Tabulated Study Reports (or Synopses) and the study reports/publications have been relocated to the section of the application in which they are discussed. As a result of this relocation, many cross-references have also been changed. The following volumes have been revised and are provided in this Amendment:

Volume 1.1	Item 1. Application Index
Volume 1.2	Item 2. Labeling
Volume 1.3	Item 3. Application Summary
Volume 1.12	Item 6. Human Pharmacokinetics and Bioavailability
Volumes 1.15 - 1.44	Item 8. Clinical Data Section
Volumes 1.45 - 1.74	Item 10. Statistical Data Section

In Items 1, 2, 3 and 6, only those sections of the item that cross-referenced Item 8/10 have been changed to reflect the new locations.

Internal Meeting Minutes

Date: October 29, 1997 **Time:** 8:30 AM - 9:30 AM **Location:** Parklawn 17B-43

NDA 20-874 **Drug Name:** Cyclo-Provera (medroxyprogesterone acetate and estradiol cypionate injectable suspension)

Type of Meeting: filing meeting

Meeting Chair: Heidi Jolson, M.D., M.P.H.

Meeting Recorder: Christina Kish

FDA Attendees:

Heidi Jolson, M.D., M.P.H. - Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP;HFD-580)

Christine Mauck, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)

Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

Robert SeEVERS, Ph.D. - Chemist, DNDCII @ DRUDP (HFD-580)

Alexander Jordan, Ph.D. - Pharmacology Team Leader, DRUDP (HFD-580)

Angelica Dorantes, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Christina Kish - Project Manager, DRUDP (HFD-580)

Meeting Objectives:

To determine fileability of this new drug application. Cyclo-Provera is a one month injectable contraceptive which allows for regular monthly menstruation

Discussion Points:

- Clinical
 - the application is fileable, review to be initiated January 1998
 - studies were carried out by the World Health Organization (WHO)
 - a total of 32 clinical trials were carried out, three of which were pivotal
 - 17,000 women were enrolled in the trials with a total of 145,000 cycles recorded
 - this product is currently marketed in 20 other countries
 - clinical trials were completed in the 80's; there is question of why the sponsor waited until now to submit this application for review
 - case report forms for the study centers in Egypt and China are "not available" however the data is recorded on diskette
 - this application has a very low rate of pregnancy (5 recorded with an extra 2 listed as unresolved)
 - there was a 70% continuance rate for this trial; the dropout rate and loss to follow-up is low

- Chemistry
 - the application is fileable, review to be initiated in January
 - 2 Drug Master Files cited in the NDA do not belong with this NDA (sponsor has confirmed this)
 - manufacturing sites are all located in Michigan, the establishment inspection reports are expected to be returned very shortly
 - the word Cyclo in the tradename may be problematic to the nomenclature committee
- Toxicology
 - the application is fileable
- Clinical Pharmacology and Biopharmaceutics
 - the application is fileable
- Microbiology
 - the application is fileable (confirmed via e-mail)
- Statistics (post meeting discussion)
 - the application is fileable
 - request location of study reports from sponsor
 - request sponsor submit a more detailed index of all volumes submitted
 - request sponsor submit an analysis of the multi-study pivotal trial by ethnicity

Decisions Reached:

- application will be filed November 26, 1997
- sponsor will be requested to submit the items delineated by statistics

Unresolved Issues:

Action Items:

<u>Item</u>	<u>Person responsible</u>	<u>Time frame</u>
call sponsor re: requested items	C. Kish	10/29/97

S

Minutes Preparer

11/21/97

S

Concurrence, Chair

11/24/97

Post-meeting Note: Sponsor contacted and additional material requested, sponsor will submit as soon as possible.

NDA 20-874
Cyclo-Provera
October 29, 1997

Page 3

cc:

Orig. NDA

HFD-580

HFD-580/HJolson/CMauck

HFD-580/JMercier/LPauls

HFD-580/CKish/10.29.97/n20847.45d

concurrences: ADorantes 11.13.97/HJolson 11.13.97/LPauls 11.12.97/AJordan 11.17.97/RSeEVERS
11.17.97/MRhee 11.17.97

no response: CMauck

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: 10/23/97
<p>I called Mr. Chambers to check on a two DMFs for _____ which are listed in the NDA as being referenced and for which letters of authorization are included, because I could not find any actual reference to what the two _____ sites were doing. Mr. Chambers checked on it and told me that the DMFs were included in the submission in error. I thanked him for this information.</p> <p style="text-align: center;">S/</p> <p style="text-align: center;">10/23/97</p> <p>Name: Robert H. Seevers HFD-580</p>	<p>NDA #: 20-874</p> <p>Telecon/Meeting initiated by:</p> <p><input type="radio"/> Applicant/Sponsor <input checked="" type="radio"/> FDA</p> <p>By: Telephone</p> <p>Product Name: Cyclo-Provera™</p> <p>Firm Name: Pharmacia & Upjohn</p> <p>Name and Title of Person with whom conversation was held: Jamie Chambers</p> <p>Phone: 616-833-1397</p>

APPEARS THIS WAY
ON ORIGINAL

/S/

NDA 20-874

OCT - 3 1997

Pharmacia & Upjohn
Attention: Mr. James H. Chambers
Regulatory Manager, U.S. Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 49001

Dear Mr. Chambers:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Cyclo-Provera (medroxyprogesterone acetate/estradiol cypionate)
Contraceptive Injection, 25 mg medroxyprogesterone acetate and 5 mg
estradiol cypionate

Therapeutic Classification: Standard

Date of Application: September 25, 1997

Date of Receipt: September 26, 1997

Our Reference Number: 20-874

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on November 25, 1997, in accordance with 21 CFR 314.101(a).

If you have any questions, please contact Christina Kish, Consumer Safety Officer, at (301) 827-4260.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely,

/S/

10/3/97

Lana L. Pauls, M.P.H.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

Original NDA 20-874

HFD-580/Div. Files

HFD-580/CSO/C.Kish

HFD-580/Rarick/Jolson/Mauck/Rhec/Seevers/Jordan/Kammerman/Dorantes/Cooney

DISTRICT OFFICE

HFD-580/CKish/10.2.97/n20874.ak

concurrency:LPauls 10.3.97

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY
ON ORIGINAL



Pharmacia & Upjohn

Office of:
James H. Chambers
Regulatory Manager
U.S. Regulatory Affairs

Telephone No. (616) 833-1397
Facsimile No. (616) 833-8237

September 25, 1997

Lisa D. Rarick, M.D.
Division of Reproductive & Urological Drug Products HFD-580
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20857

RE: NDA 20-874
CYCLO-PROVERA™ Contraceptive Injection
(Medroxyprogesterone Acetate and
Estradiol Cypionate)

ORIGINAL NEW DRUG APPLICATION

Dear Dr. Rarick,

Under the provisions of 21 CFR 314.50, we are submitting a New Drug Application for CYCLO-PROVERA™ Contraceptive Injection (medroxyprogesterone acetate and estradiol cypionate injectable suspension) for the prevention of pregnancy.

The cumulative data contained within this application represents use in over 17,000 women with the total exposure of over 145,000 cycles. Three large, adequate and well-controlled studies conducted by the World Health Organization (WHO) form the basis of this application. Thirty-eight supportive studies, many from literature, provide additional information regarding the pharmacology and safety and efficacy of this product. This body of data, together with historical data on the failure rates of other commonly-used contraceptives, demonstrates the efficacy and safety of CYCLO-PROVERA in the prevention of pregnancy.

This application is comprised of 120 total volumes. All volumes are sequentially numbered 1.1 (Index) to 1.120. Item 7 Microbiology appears at the end of the application in Volumes 1.119 and 1.120. Since Items 13, 14, and 16-18 are brief, they are provided for convenience in volume 1.1 immediately behind the 356h form. The format and content of this application was discussed at two pre-NDA meetings held on June 6, 1995, between the former Upjohn Company and FDA and on January 17, 1997, between Pharmacia & Upjohn and FDA.

CYCLO-PROVERA™ Contraceptive Injection
New Drug Application
September 25, 1997

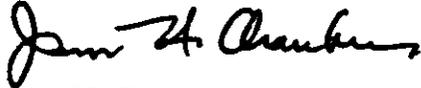
There are currently two ongoing studies in the United States under IND 52,624. A multi-center comparative study of safety and efficacy (Protocol M/5415/0004) has a target enrollment of 1200 females of child-bearing potential and a pharmacokinetic/pharmacodynamic multiple dose study (Protocol M/5415/0006) has a target enrollment of 16 surgically sterile females. Each of these studies is still currently accruing patients. It is unlikely that a substantial amount of new data will be available and summarized for the 4-month safety update as required in 21 CFR 314.50(d)(5)(vi)(b). Therefore, Pharmacia & Upjohn would like to request a waiver of the requirement for this safety update.

In accordance with the Prescription Drug User Fee Act of 1992, a User Fee in the amount of \$102,000 has been mailed to Mellon Bank.

If you have any questions regarding the contents of this submission, please contact James H. Chambers at (616) 833-1397. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY



James H. Chambers, Regulatory Manager
U.S. Regulatory Affairs

JHC:law

APPEARS THIS WAY
ON ORIGINAL

Pre-NDA

for monthly inj.

January 14, 1997

Upjohn

Memo of pre-Meeting

Attendees:

Lisa Rarick, M.D.

Ridgely Bennett, M.D.

Angelica Dorantes, Ph.D.

Lisa Kammerman, Ph.D.

Kate Meaker, Ph.D.

Christina Kish

Background:

The Division received a background package in support of a meeting between the sponsor and this Division. A draft protocol for a Phase a 3 study was submitted. It was noted that the sponsor anticipates submitting an NDA in the very near future. However, very little is known at present about the state of the data the sponsor plans to submit. The following questions were raised during the pre-meeting.

1. **The proposed NDA**
 - a. When do you plan to submit the NDA
 - b. Please clarify what you are proposing to submit and use as pivotal trials in support of an NDA
 - c. What do you propose to submit in support of the pharmacokinetics portion of an NDA
 - d. What do you plan to do regarding bridging studies between the product used in the pivotal trials and the product to be marketed here
 - e. What other trials do you plan to perform, and how do you plan to use them
 - f. Will you be able to submit case reports for serious adverse events and pregnancies
 - g. Regarding the pivotal trials it seems that during the patient visits, if several adverse event were reported by a single patient only two were recorded:
 1. is this correct
 2. is there any way to capture the rest of the adverse events
 3. how was the determination made regarding which adverse events to include

for monthly inj.

- h. As part of the NDA submission we need
 - 1. Subheadings with information summarized in the NDA submission, for example effects on carbohydrate metabolism, lactation, return to fertility etc. on this specific drug
 - 2. Case reports for all pregnancies and serious adverse events
 - 3. Summaries of all the published literature you are planning to submit, including extracting appropriate data to support the conclusions you assert
 - 4. Information regarding potential drug accumulation
 - 5. An intent-to-treat analysis

2. Proposed IND protocol

- a. What is the purpose of your proposed IND study
- b. What claims do you plan to make by performing this trial
- c. Is your study going to last 52 weeks or 48 weeks, if 48 weeks why not 52 weeks
- d. What sorts of statistical analysis are you planning to perform on this study
- e. Will any pharmacokinetics information be collected and analyzed

cc:

HFD-580/Contraceptive not oral Div. File

HFD-580/CMafk

MEETING ATTENDEES

HFD-580/CKish/1.15.97/_____pmm

APPEARS THIS WAY
ON ORIGINAL

pre-NDA

(medroxyprogesterone acetate and estradiol cypionate) Sterile Suspension for Injection

June 6, 1995
The Upjohn Company

MEMORANDUM OF MEETING
(pre-NDA)

Industry Participants:

Dr. R. F. Carlson (Director, Clinical Development, Upjohn)
Dr. J. P. Jacobs (Clinical Monitor, Clinical Development, Upjohn)
Dr. D. J. Stalker (Clinical Pharmacokinetics, Upjohn)
Dr. F. G. Ogrinc (Biostatistician, Upjohn)
Dr. K. M. Cookson (Toxicologist, Upjohn)
Dr. M. D. VanArendonk (Director, Specifications Development, Upjohn)
Dr. H. J. de Konig Gans (Director, Regulatory Affairs, Upjohn)
Dr. G. W. Perkin (President, PATH)
Mr. M. D. Burdick (Regulatory Manager, Regulatory Affairs, Upjohn)
Ms. D. L. Smith (Project Manager, Upjohn)

FDA Participants:

Dr. S. Sobel (Division Director, HFD-510)
Dr. P. Corfman (Grp. Ldr., HFD-510)
Dr. B. Stadel (MO, HFD-510)
Dr. C. Cropp (MO, HFD-510)
Dr. R. Bennett (MO, HFD-510)
Dr. A. Bey (MO, HFD-510)
Dr. K. Raheja (Pharmacologist, HFD-510)
Dr. A. Dorantes (Biopharmaceutics, HFD-426)
Dr. L. L. Stockbridge (CSO, HFD-510)

Purpose: The sponsor has requested this meeting to discuss the development of Cyclo-Provera and the proposed clinical section of an NDA.

Introduction

Cyclo-Provera (_____) is a monthly injectable contraceptive containing 25 mg medroxyprogesterone acetate and 5 mg estradiol cypionate in an 0.5 ml suspension. Preliminary animal and clinical data for this application is accessible through W.H.O. There have been no new studies done by the sponsor. The Division met with PATH on November 15, 1993, to discuss the preliminary studies and Phase III studies (see Memorandum of Meeting November 15, 1993). The sponsor distributed handouts of the overheads used (attached).

Clinical

The sponsor presented an overview of the clinical trials done by W.H.O. There are limitations to the data base. There are no comments on the study reports (i.e., the reports only carry coded information). There is no safety data beyond one year.

Dr. Stadel commented that the safety data uses events, rather than patients, for tabulation. This is very difficult to analyze because it does not account for the individual patient who may have zero, one, or more adverse events. The sponsor said that tabulation by patient will be done in the Integrated Summary of Safety.

Dr. Bennett asked whether or not there were anaphylactic events and, if so, how they were coded. There had been no such events reported. This is of concern because there have been reports of this serious reaction with Depo-Provera. The sponsor will check to make sure if there was a code for it.

Dr. Bennett asked what type of data were used to support the claim of rapid return of ovulation. There are pharmacokinetics data used to support this claim.

Since failures with Depo-Provera are greater than that predicted by the original clinical trials, there is concern over how pregnancies will be reported in the submission for Cyclo-Provera. All pregnancies must be reported. Because the sponsor does not have access to the Egyptian or Chinese case reports, the only case reports which will be available to Dr. Bennett will be the reports from Geneva.

Dr. Corfman asked for data on dose ranging in support of the use of the "lowest effective dose".

Pharmacology

There have been no preclinical studies done with Cyclo-Provera. The sponsor had planned to use studies done for Depo-Provera in place of this.

Biopharmaceutics

An overview of pharmacokinetics findings is given in the handout on page 17. The formulation used in the clinical studies is the same as that which will be marketed. Dr. Dorantes asked for a more sensitive assay than RIA. The sponsor said that _____ could be used. Validation and assay performance data will also be provided.

The issue of population pharmacokinetics/pharmacodynamics analyses (for weight, height, etc.) was discussed. The sponsor said that there did not seem to be an effect of body mass on efficacy.

Discussion

Dr. Bennett asked for data on the serum levels of medroxyprogesterone acetate which mark the return of ovulation. A question is how long it takes the woman to become pregnant after taking Cyclo-Provera. The sponsor said they were not aware of such data. Dr. Bennett remembered at least one publication which examined this.

The lack of case report forms is a concern. Dr. Bennett would like to see all pregnancy case report forms and all serious reaction case report forms. It is understood that the latter would be retrospective.

The sponsor was told that the data was weak. There is published data that needs to be researched to make the application a bit stronger. This includes data on histology, teratogenicity, liver function, carbohydrate metabolism, lactation, and return to fertility. The sponsor inquired about the possibilities for a Phase IV agreement to answer some of these questions. They were told that this may be a possibility.

Conclusion and Recommendations

- Dr. Dorantes will send the sponsor a guidance document for the organization of the Pharmacokinetics section of the NDA.
- Dr. Bennett found a reference regarding the return of fertility after Cyclo-Provera injection (Koetsawang. 1978. *Int. J. Gynecol. Obstet.* 16: 61-64). Dr. Stockbridge relayed the information to the sponsor.
- The sponsor will have to address dose-ranging and give provide support for a "lowest possible dose".
- Dr. Raheja will examine the preclinical studies submitted for Depo-Provera and determine whether or not this will can suffice for the Cyclo-Provera application.

/S/

Dr. Lisa L. Stockbridge, CSO

ATTACHMENT

cc: HFD-510, Contraceptives, Not Oral
HFD-510/YJohnson/FDA Participants
HFD-426/ADorantes
HFD-510/LStockbridge/6.6.95\m50606.min

APPEARS THIS WAY
ON ORIGINAL

Concurrences: RBennett 6.12/ABey 6.14/CCropp/BStadel/PCorfman/KRaheja 6.28/
ADorantes/SSobel 6.30/EGalliers 7.13.95

3 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

NDA 20-874

Lunelle™ Monthly Contraceptive Injection (medroxyprogesterone acetate and estradiol cypionate)
Pharmacia & Upjohn

DSI Audit

No review necessary for this review cycle.

/S/

9/27/00

Jennifer Mercier, Regulatory Project Manager
HFD-580

APPEARS THIS WAY
ON ORIGINAL

medroxyprogesterone acetate
and estradiol cypionate injection
Pharmacia and Upjohn

Exclusivity Checklist

An exclusivity checklist has not been filled out because this application will be issued a not approval letter.

APPEARS THIS WAY
ON ORIGINAL

NDA 20-874
Lunelle™ Monthly Contraceptive Injection
(medroprogesterone acetate and estradiol cypionate)

Methods Validation

Methods have not yet been validated.

**APPEARS THIS WAY
ON ORIGINAL**

NDA 20-874
Lunelle™ Monthly Contraceptive Injection
(medroprogesterone acetate and estradiol cypionate)

Safety Update Review

Safety Update dated August 18, 1999, was reviewed in Medical Officer Review dated September 23, 1999. (see Page 31)

**APPEARS THIS WAY
ON ORIGINAL**

NDA 20-874
Lunelle™ Monthly Contraceptive Injection
(medroprogesterone acetate and estradiol cypionate)

Safety Update Review

Safety Update dated July 16, 1998, was reviewed in Medical Officer Review dated September 3, 1998. (see Page 37)

**APPEARS THIS WAY
ON ORIGINAL**

NDA 20-874
Lunelle™ Monthly Contraceptive Injection
(medroprogesterone acetate and estradiol cypionate)

Carcinogenicity Review

N/A

**APPEARS THIS WAY
ON ORIGINAL**

NDA 20-874
Lunelle™ Monthly Contraceptive Injection
(medroprogesterone acetate and estradiol cypionate)

CAC/Exec Committee Review

N/A

APPEARS THIS WAY

NDA 20-874
Lunelle™ Monthly Contraceptive Injection
(medroprogesterone acetate and estradiol cypionate)

Abuse Liability Review

N/A

**APPEARS THIS WAY
ON ORIGINAL**

medroxyprogesterone acetate
and estradiol cypionate injection
Pharmacis and Upjohn

Advisory Committee Minutes

This application has not been the subject of an Advisory Committee Meeting.

APPEARS THIS WAY
ON ORIGINAL

**OFFICES OF DRUG EVALUATION
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST**



NDA 20-874

Drug: _____

Applicant: Pharmacia GbjokChem/Ther/other Types: 4S

CSO/PM: Kiosk Phone: 301 227 4271 HFD-580

USER FEE GOAL DATE: 7/20/98 DATE CHECKLIST COMPLETED: _____

Arrange package in the following order (include a completed copy of this CHECKLIST): _____ Check or Comment _____

1. ACTION LETTER with supervisory signatures
Are there any Phase 4 commitments? AP NA AE NA NA
Yes _____ No _____
2. Have all disciplines completed their reviews?
If no, what review(s) is/are still in draft? Yes _____ No _____
3. LABELING (package insert and carton and container labels).
(If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.) Draft 9/20/97
Revised Draft _____
Final _____
4. PATENT INFORMATION
5. EXCLUSIVITY CHECKLIST
6. PEDIATRIC PAGE (all NDAs)
7. DEBARMENT CERTIFICATION (Copy of applicant's certification for all NDAs submitted on or after June 1, 1992)
8. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES
If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status.
If no audits were requested, include a memo explaining why. NA case but report pending
9. REVIEWS & MEMORANDA:

DIVISION DIRECTOR'S MEMO	If more than 1 review for any	
GROUP LEADER'S MEMO	1 discipline, separate reviews	<u>9/8/98</u>
MEDICAL REVIEW	with a sheet of colored paper.	<u>9/3/98</u>
SAFETY UPDATE REVIEW	Any conflicts between reviews	<u>9/3/98</u>
STATISTICAL REVIEW	must have resolution documented	<u>9/3/98</u>
BIOPHARMACEUTICS REVIEW		<u>7/1/98</u>
PHARMACOLOGY REVIEW (Include pertinent IND reviews)		<u>12/23/97</u>
Statistical Review of Carcinogenicity Study(ies)		<u>NA</u>
CAC Report/Minutes		<u>NA</u>
CHEMISTRY REVIEW		<u>4/21/98 & 7/27/98</u>
Labeling and Nomenclature Committee Review Memorandum		
Date EER completed _____ (attach signed form or CIRT's printout)	OK _____ No _____	
FUR needed _____ FUR requested _____	Yes (attach) _____ No _____	
Have the methods been validated?		
Environmental Assessment Review / FONSI	Review <u>NA</u> FONSI _____	
MICROBIOLOGY REVIEW		<u>3/7/98</u>
What is the status of the monograph?		<u>NA</u>
10. CORRESPONDENCE, MEMORANDA OF TELECONS, and FAXes
11. MINUTES OF MEETINGS
Date of End-of-Phase 2 Meeting: NA
Date of pre-NDA Meeting: 6/6/95
12. ADVISORY COMMITTEE MEETING MINUTES
or, if not available, 48-Hour Info Alert or pertinent section of transcript. Minutes NA Info Alert _____
Transcript _____ No mtg _____
13. FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS NA
14. If approval letter, has ADVERTISING MATERIAL been reviewed?
If no and this is an AP with draft labeling letter, has advertising material already been requested? NA Yes _____ No _____
Yes, documentation attached _____
No, included in AP ltr _____

OFFICES OF DRUG EVALUATION
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST

Page 2

15. INTEGRATED SUMMARY OF EFFECTIVENESS (from NDA)

16. INTEGRATED SUMMARY OF SAFETY (from NDA)

revision: 5/14/96

APPEARS THIS WAY
ON ORIGINAL

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA <u>20-874</u> / SE _____ - _____		
Drug <u>Lunelle™ Monthly Contraceptive Injection</u> Applicant <u>Pharmacia & Upjohn</u>		
RPM <u>Jennifer Mercier</u>		Phone <u>301-827-4260</u>
505(b)(1)		
505(b)(2)	Reference listed drug <u>Medroxyprogesterone acetate and estradiol cypionate</u>	
Fast Track	Rolling Review	Review priority: <u>(S) P</u>
Pivotal IND(s) _____		
Application classifications:		PDUFA Goal Dates:
Chem Class <u>4S</u>	Primary <u>October 7, 2000</u>	
Other (e.g., orphan, OTC) _____	Secondary _____	

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- ◆ User Fee Information: User Fee Paid
 User Fee Waiver (attach waiver notification letter)
 User Fee Exemption

- ◆ Action Letter..... (A) P AE NA

- ◆ Labeling & Labels

FDA revised labeling and reviews.....	X
Original proposed labeling (package insert, patient package insert)	X
Other labeling in class (most recent 3) or class labeling.....	X
Has DDMAC reviewed the labeling?	<u>Yes</u> (include review) No
Immediate container and carton labels	X
Nomenclature review	X

- ◆ Application Integrity Policy (AIP) Applicant is on the AIP. This application is X is not on the AIP.

Exception for review (Center Director's memo).....	N/A
OC Clearance for approval.....	N/A

- ◆ Safety Update review(s) X
- ◆ Pediatric Information
 - Waiver/partial waiver (Indicate location of rationale for waiver) Deferred Pediatric Page..... X
 - Pediatric Exclusivity requested? Denied Granted Not Applicable
- ◆ Statistical review(s) and memoranda X
- ◆ Biopharmaceutical review(s) and memoranda X
- ◆ Abuse Liability review(s) N/A
- Recommendation for scheduling N/A
- ◆ Microbiology (efficacy) review(s) and memoranda X
- ◆ DSI Audits N/A
- Clinical studies bioequivalence studies

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ CMC review(s) and memoranda X
- ◆ Statistics review(s) and memoranda regarding dissolution and/or stability N/A
- ◆ DMF review(s) X
- ◆ Environmental Assessment review/FONSI/Categorical exemption N/A
- ◆ Micro (validation of sterilization) review(s) and memoranda X
- ◆ Facilities Inspection (include EES report)
 - Date completed _____ Acceptable Not Acceptable
- ◆ Methods Validation Completed Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ Pharm/Tox review(s) and memoranda X
- ◆ Memo from DSI regarding GLP inspection (if any) N/A

- ◆ Statistical review(s) of carcinogenicity studies N/A
- ◆ CAC/ECAC report N/A

**APPEARS THIS WAY
ON ORIGINAL**

ODE III ACTION PACKAGE TABLE OF CONTENTS

Application # 20-874 Drug Name: Lunelle™ Monthly Contraceptive Injection
 Applicant: Pharmacia & Upjohn Chem./Ther. Type: 4S
 CRO/PM: Jennifer Mercier Phone: 7-4260 HFD- 580
 Original Application Date: _____ Original Receipt Date: _____

CURRENT USER FEE GOAL DATE: 10/17/99 Date Table of Contents Completed: _____

Section A: Administrative Information

X (completed),
N/A (not applicable),
or Comment

Section	Description	Status
Tab A-1	Action Letter(s) Current Action: <u>AE</u>	X
Tab A-2	Phase 4 Commitments:	
	a. Copy of applicants communication committing to Phase 4.....	N/A
	b. Agency Correspondence requesting Phase 4 Commitments	N/A
Tab A-3	FDA revised Labels & Labeling and Reviews:	
	a. Package Insert	N/A
	b. Immediate Container and Carton Labels	X
Tab A-4	Original Proposed Labeling	X
Tab A-5	Foreign Labeling:	
	a. Foreign Marketing History.....	N/A
	b. Foreign Labeling and Review(s)	N/A
Tab A-6	Labeling and Nomenclature Committee's Tradename Review	X
Tab A-7	Summary Memoranda (e.g., Division Director, Group Leader, Office).....	
Tab A-8	Copy of Patent Statement.....	X
	Exclusivity Checklist (and any requests for exclusivity)	X
	Debarment Statements.....	X
Tab A-9	Correspondences, Faxes, & Telecons.....	X
Tab A-10	Minutes of Meetings:	
	a. End-of-Phase II meeting	N/A
	b. Pre-NDA meeting(s) <u>6/6/95/1/14/97</u>	X
	c. Filing meeting	X
	d. Other meetings... <u>and telecons</u>	X
Tab A-11	Advisory Committee Meeting:	
	a. Questions Considered by the committee	N/A
	b. List of Attendees	N/A
	c. 24 hour alert memorandum	N/A
Tab A-12	Project Management Administrative Information (optional).....	X

BEST POSSIBLE COPY

ODE III ACTION PACKAGE TABLE OF CONTENTS (continued)

Application # _____ Drug Name: _____

Section B:

Clinical Information

X (completed),
N/A (not applicable),
or Comment

Tab B-1	Clinical Reviews and Memoranda.....	X
Tab B-2	Safety Update Reviews.....	X
Tab B-3	Pediatric Page.....	X
Tab B-4	Statistical (Clinical) Review and Memoranda.....	X
Tab B-5	Biopharmaceutics Review and Memoranda.....	X
Tab B-6	Abuse Liability Review.....	N/A
Tab B-7	DSI Audits.....	
Tab B-8	Summary of Efficacy (from the summary volume of the application).....	
Tab B-9	Summary of Safety (from the summary volume of the application).....	

Section C:

Chemistry, Manufacturing, and Controls (CMC) Information

X (completed),
N/A (not applicable),
or Comment

Tab C-1	CMC Reviews and Memoranda.....	X
Tab C-2	DMF Reviews.....	X
Tab C-3	EA Reviews/FONSI.....	N/A
Tab C-4	Micro Review (validation of sterilization).....	X
Tab C-5	Statistical Review of drug stability.....	N/A
Tab C-6	Inspection of facilities => Decision: 10/29/97 Date: _____	X
Tab C-7	Methods Validation Information.....	N/A

Section D:

Pharmacology/Toxicology Information

X (completed),
N/A (not applicable),
or Comment

Tab D-1	Pharmacology/Toxicology Reviews and Memoranda.....	X
Tab D-2	Carcinogenicity Review (statistical).....	N/A
Tab D-3	CAC/Executive Committee Report.....	N/A

ADDITIONAL NOTES:



Pharmacia & Upjohn

Office of:
P.K. Narang, Ph.D., F.C.P.
Liaison Director, New Drugs
Global Regulatory Affairs

Telephone No. (616) 833-9896
Facsimile No. (616) 833-8237

October 13, 1999

Lisa Rarick, M.D.
Division of Reproductive and Urologic Drug Products, HPD-580
Center for Drug Evaluation and Research
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-874
Lunelle™ Monthly Contraceptive Injection
(Medroxyprogesterone acetate and Estradiol cypionate
Injectable Suspension)

GENERAL CORRESPONDENCE
LABELING: Physician and Patient Insert
Phase IV Commitment

Dear Dr. Rarick

Per our teleconference of October 12, 1999, Pharmacia and Upjohn (P&U) is pleased to submit the following labeling pieces for LUNELLE™ Monthly Contraceptive Injection. We would also like to note that all changes recommended yesterday by the Division and Dr. S. Allen have been duly incorporated. Thus, this submission contains a copy of what we trust will be final (agreed to for PI) labeling.

1. Physician Insert Labeling (Revised; P&U: dated 10/12/99)
2. Patient Insert Labeling (Revised, P&U: dated 10/12/99)

An electronic copy of items 1 and 2 was also sent to Ms. Mercier earlier today. Data supporting the inclusion of the statement on weight gain/loss Drs. Allen and Hixon asked for is also provided (see Attachment A). A "™" symbol has been placed after every occurrence of Lunelle in the PI and PPI as advised by Ms. Mercier on October 13, 1999.

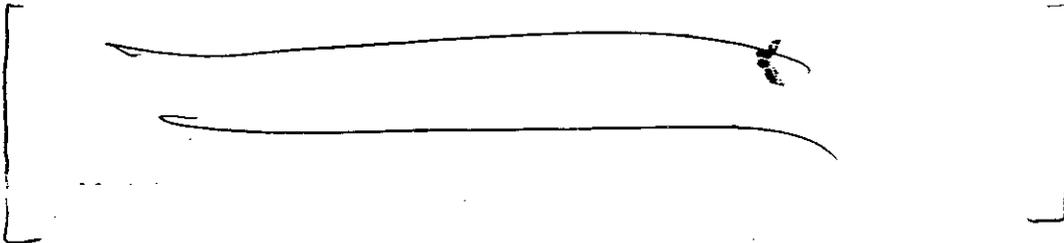
Labeling: Non-Insert

P&U submitted the 'Non-insert labeling' yesterday addressing all the recommendations of the reviewer. Ms. Mercier and Dr. David Lin called and informed us today (Oct 13) that the non-insert

labeling was acceptable, however we must show where the LOT# and EXP date would be placed on the label, when printed on-line (see Attachment B).

Phase IV Commitment:

Further, per your request, P&U will commit to one or more Phase IV studies to assess potential benefits of the combination product (including the estrogen). We, however, confront a few practical issues in how best to document such a benefit (or its impact), in addition to the data documenting the cyclic pattern of one monthly bleeding/spotting episode in >70% of women (study data /0004) shared with you. We would reassess the issue around the bleeding patterns definitions and how best to approach the selection of an appropriate endpoint. It is anticipated that more thought/discussion and Division's guidance may allow us to consider arenas other than the three noted below, along with refining specific study design issues (doses, duration, comparators, endpoints, etc.). However, based on our limited discussion P&U proposes the following three arenas may be useful to document the benefit of added estrogen:



Bone Mineral Density: An evaluation of the effects of LUNELLE™ Monthly Contraceptive Injection on bone mineral density.

P&U commits to seek Division's guidance by further discussion and finalization of specific protocol aspects within 6 months from the date of the 'approval' letter. P&U will seek agreement with FDA on key studies/designs prior to initiation of these trials.

If you have any questions regarding this submission, please contact me at (616) 833-9896. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

P.K. Narang, Ph.D., F.C.P.
Director

PKN:SEH
Attachments

cc: Jennifer Mercier (Desk Copy)

APPEARS THIS WAY
ON ORIGINAL

39 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

Appendix B
(EER)

APPEARS THIS WAY
ON ORIGINAL

14-APR-2000

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Page 1 of 2

Application: NDA 20874/000
Stamp: 26-SEP-1997
Regulatory Due: 07-JUN-2000
Applicant: PHARMACIA AND UPJOHN
7000 PORTAGE RD
KALAMAZOO, MI 490010199
Priority: 4S
Org Code: 580

Action Goal:
District Goal: 27-MAY-1998
Brand Name: []
Estab. Name:
Generic Name: ESTRADIOL
CYPIONATE/MEDROXYPROGESTERONE
Dosage Form: (SUSPENSION)
Strength: 5 MG/25 MG

Application Comment:

FDA Contacts: ID = 115760, Project Manager
R. SEEVERS (HFD-120) 301-594-2850, Review Chemist
M. RHEE (HFD-590) 301-827-4237, Team Leader

Overall Recommendation: on 14-OCT-1999 by S. FERGUSON (HFD-324) 301-827-0062
ACCEPTABLE on 14-APR-2000 by S. FERGUSON (HFD-324) 301-827-0062
ACCEPTABLE on 10-NOV-1997 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment:



DMF No: AADA:
Responsibilities:
Profile: GSP OAI Status: NONE

Estab. Comment: THIS SITE STERILIZES BOTH OF THE DRUG SUBSTANCES (on 29-OCT-1997 by R. SEEVERS (HFD-120) 301-594-2850)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-OCT-1997				DAMBROGIOJ
OC RECOMMENDATION	29-OCT-1997			ACCEPTABLE BASED ON PROFILE	FERGUSONS
SUBMITTED TO OC	10-APR-2000				LINDAV
OC RECOMMENDATION	11-APR-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: 1810189

4 PHARMACIA AND UPJOHN CO
7000 PORTAGE ROAD
KALAMAZOO, MI 49001

DMF No: 4266 4975 5047 AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE MANUFACTURER
Profile: CSN OAI Status: NONE

Estab. Comment: THIS SITE MANUFACTURES BOTH DRUG SUBSTANCES. IT ALSO MANUFACTURES THE DRUG PRODUCT FROM THE STERILIZED DRUG SUBSTANCES (on 29-OCT-1997 by R. SEEVERS (HFD-120) 301-594-2850)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-OCT-1997				SEEVERSR
OC RECOMMENDATION	29-OCT-1997			ACCEPTABLE BASED ON PROFILE	FERGUSONS
SUBMITTED TO OC	10-APR-2000				LINDAV
OC RECOMMENDATION	11-APR-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Profile: SVS OAI Status: NONE

14-APR-2000

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Page 2 of 2

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-OCT-1997				DAMBROGIOJ
SUBMITTED TO DO	29-OCT-1997	10D			DAMBROGIOJ
DO RECOMMENDATION	07-NOV-1997			ACCEPTABLE BASED ON FILE REVIEW	MROBINSO
DET-DO COMPLETED A COMPREHENSIVE GMP INSPECTION OF PROFILE CLASS SVS (STERILE FILLED SMALL VOLUME PARENTERALS) DATED 10/20-30/97. NO FDA-483 WAS ISSUED AND THE REPORT WILL BE CLASSIFIED NAI.					
OC RECOMMENDATION	10-NOV-1997			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ FERGUSONS
OC RECOMMENDATION	14-OCT-1999			EIR REVIEW CONCUR W/DISTRICT	
SIGNIFICANT GMP DEFICIENCIES					
SUBMITTED TO OC	10-APR-2000				LINDAV
SUBMITTED TO DO	11-APR-2000	10D			DAMBROGIOJ
DO RECOMMENDATION	13-APR-2000			ACCEPTABLE BASED ON FILE REVIEW	MROBINSO
GMP EI MARCH 20-31, 2000 CONFIRMED CORRECTIONS TO THE ASEPTIC FACILITY. THE EIR WILL BE CLASSIFIED VAI.					
OC RECOMMENDATION	14-APR-2000			ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS

Teleconference Minutes

Date: October 3, 2000

Time: 3:15 – 4:00 PM

Location: Parklawn; 17B-43

NDA 20-874

Drug: Lunelle™ Monthly Contraceptive Injection
(medroxyprogesterone acetate/ethinyl estradiol)

Indication: contraceptive

Sponsor: Pharmacia & Upjohn

Type of Meeting: Labeling

FDA Attendees:

Dena Hixon, M.D. – Medical Officer, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Scott Monroe, M.D. – Medical Officer, DRUDP (HFD-580)

Jennifer Mercier, B.S. – Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:

Roger Garceau, M.D. - Clinical Development, Pharmacia & Upjohn

Charles Wajszczuk, M.D. - Clinical Development, Pharmacia & Upjohn

Henk deKoning Gans, M.D. - Clinical Development, Pharmacia & Upjohn

P.K. Narang, Ph.D. - Global Regulatory Affairs, Pharmacia & Upjohn

Carl DeJuliis, M.S. - Global Reg. Affairs, Pharmacia & Upjohn

Cynthia Greenwald, M.S. - Biostatistics, Pharmacia & Upjohn

Chris Bilkey - Global Business Management, Pharmacia & Upjohn

Colette Andrea - Global Business Management, Pharmacia & Upjohn

Meeting Objective: To negotiate final labeling for this drug product.

Decisions made:

- the Division will require one phase 4 commitment to study bone mineral density study
- the sponsor agrees to submit the protocol within six months post-approval and receive Division agreement prior to study initiation
- the sponsor agrees that the primary endpoint of this study will be modified to '% change from baseline' and the test between the arms will consider the sensitivity related to measurement error
- the sponsor also agrees that the protocol will not propose to impute any missing DXA data
- Labeling: See attached label.

157
Minutes Preparer

[151]
Concurrence, Chair

c:
Original NDA
HFD-580/DivFile
HFD-580/Rumble/Mercier
HFD-580/Allen/Shames/Hixon/Monroe

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

33 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

Electronic Mail Message

10/4/00 4:08:32 PM.

From: Prem.K.Narang

(Prem.K.Narang@am.pnu.com)

To: mercierj

(mercierj@A1)

Subject: NDA 20-874 Cyclo-Provera

Hi Jen

Here is the modified cover letter as you requested this afternoon. Let me know if this addresses your needs. We are getting down to the last day. Appreciate you letting me know that action could happen tomorrow. Just advise me before you are ready to FAX. This letter has been sent by overnight mail as well and you should get the submission sent earlier this afternoon and the letter at the same time (its addressed to Dr. Allen). I have stated that this letter supersedes the previous one. Hope that is OK? let me know.

rgds

P.K.

Forward Header

Subject: NDA 20-874 Cyclo-Provera

From: Sue E Huntington at PN05PO

Date: 10/4/00 3:47 PM

The attached letter supersedes the letter included in the labeling submission sent earlier this morning and may be appended to it. Information requested by the Division is now shown in BOLD text.

October 4, 2000

Susan Allen, M.D.
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

**RE: NDA 20-874
Lunelle Monthly Contraceptive Injection
(Medroxyprogesterone acetate and Estradiol
cypionate Injectable Suspension)**

LABELING: Insert

Dear Dr. Allen

Following the agreements reached between Pharmacia and Upjohn (P&U) and the Division (Drs. Hixon and Monroe) during the teleconference at 3:30 pm on October 3, 2000, we are pleased to provide a revised (FINAL) clean copy of Physician (pi) and Patient (ppi) inserts for Lunelle Monthly Contraceptive Injection.

1. Physician Insert (Version 10.3.2000; Attachment 1)
 - pi1003.doc (clean WORD 6.0 copy)
 - pi1003.pdf (pdf file format)

2. Patient Package Insert (Version 10.3.2000; Attachment 2)
 - ppi1003.doc (clean WORD 6.0 copy)
 - ppi1003.pdf (pdf file format)

A copy of all the files noted above was also sent electronically today via e:mail to assist with an expedited final review from the Division. All files are also placed on the enclosed CD-ROM. Per our discussion, please note the corrected numbers for 'weight

change' in the Table (under Precautions). The enclosed transport media was checked using VirusScan NT (version 7) and deemed 'virus free'. Though P&U has taken needed precautions, use of a similar software by CDER is encouraged for added assurance.

We further appreciate additional clarifications provided by the Division staff regarding our Phase IV commitment. P&U was pleased to learn of your conclusion that only the bone mineral density (BMD) study will be required to fulfill this commitment to establish estrogen's benefit. Prior to study initiation, we agree to share a copy of the final (DRAFT) protocol for this study with your staff and seek feedback to ensure adequacy of design and statistical methodology. We understand and agree that the primary endpoint definition will be modified to '% change from baseline' per Division's advice and the test between the arms will consider the sensitivity related to measurement error. **We also agree that the protocol will not propose to impute any missing DXA data.** We anticipate sharing the protocol as soon as possible, and certainly sooner than 6 months post-approval action on this application.

Last but not the least, we at P&U appreciate all your thoughtful guidance and assistance afforded to us during the review of this application. Should there be any questions regarding this submission, please contact me at (616) 833-9896. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

P.K. Narang, Ph.D., F.C.P.
Director
Global Regulatory Affairs

PKN:kmv

Attachments

APPEARS THIS WAY
ON ORIGINAL

cc: Jennifer Mercier (Desk Copy)

ps: This letter from sponsor supersedes the letter included in the labeling submission sent earlier this morning and may be appended to it. The information requested by the division is now shown in the bold text above.



Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

August 9, 2000

Dr. Susan Allen, Director
Division of Reproductive and Urological Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-874
Lunelle Monthly Contraceptive Injection
(Medroxyprogesterone Acetate and
Estradiol Cypionate Injection)

General Correspondence
Corrected Version: Phase 4 Commitment

Dear Dr. Allen:

Per a telephone request from Ms. Deguia yesterday to clarify the sample size related aspects of the Phase 4 Bone Mineral density study proposal previously sent, Pharmacia and Upjohn is pleased to attach a 'corrected version' designed to assess the benefit of the added estrogen (Attachment 1). The total number of women anticipated to be enrolled is 920 for the Lunelle Monthly Contraceptive Injection (Test Arm) and 460 for the Depo-Provera Contraceptive (Reference) arms. At 2 years, we expect to have 276 and 138 evaluable women in the Test and Reference arms, respectively. We would like to bring to your attention that both "Primary End Point" and "Interim Analysis" sections have been reworded for enhanced clarity.

We apologize for the oversight at the time when this outline was last submitted and hope the Division would find this version acceptable. We look forward to sharing the "Draft Protocol" with you in due time, post-approval, to seek guidance and feedback on the adequacy of specifics. If you have any questions regarding this submission, please contact me at (616) 833-9896. Send all correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY


P.K. Narang, Ph.D., F.C.P.
Liaison Director
Global Regulatory Affairs

PKN:lmf
Attachment
cc: Ms. Eufrecina Deguia (Desk Copy)

/S/

DEPARTMENT OF HEALTH AND HUMAN SERVICES
MEMORANDUM PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date December 11, 1997
From Lisa Rarick, M.D. 12/11/97
Director, Division of Reproductive and Urologic Drug Products (HFD-580)
Subject Identification of Protocols for Inspection
NDA: 20-874
Sponsor: Pharmacia and Upjohn
Drug Name: (medroxyprogesterone acetate and estradiol cypionate)
Dosage Form: injection
To Dr. David LePay, Director
Clinical Investigations Branch, HFD-344

We have identified the protocols listed below as being important to the approval of this application.

Protocol: Multicountry study (number 83913)

Sites to be Audited: [Handwritten list of sites]

Please note, the last four sites are in _____, if the _____ site is not in close proximity to the other sites to be audited, it may be omitted.

The contact person at the sponsor's site is _____ at _____

The reviewing Medical Officer (MO) for this application is Dr. Linda Golden.

The Project Manager/CSO is Ms. Christina Kish at 301-827-4260.

The User Fee Goal Date is September 26, 1998.

The Division Action Goal Date is August 26, 1998.

cc:
NDA 20-874
HFD-580
HFD-580/LGolden/CKish
HFD-344/GTurner/CCourier/MTarosky/DLePay
concurrence:LPauls 12.9.97/HJolson 12.10.97

DEPARTMENT OF HEALTH AND HUMAN SERVICES
MEMORANDUM PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date June 29, 1998

From Lisa D. Rarick, M.D.
Director, Division of Reproductive and Urologic Drug Products (HFD-580)

Subject Identification of Protocols for Inspection
NDA: 20-874
Sponsor: Pharmacia and Upjohn
Drug Name: _____
Dosage Form: tablet

To Dr. David Lepay
Director, Division of Scientific Investigations, HFD-344

6/29/98
LS

We have identified the protocols listed below as being important to the approval of this application.

Multicountry Study; WHO Project 83913

[_____]

[_____]

** should be contacted at site

[_____]
[_____]

The reviewing Medical Officers (MOs) for this application are Drs. Julian Safran and Susan Allen.

The Project Manager is Ms. Christina Kish at 301-827-4260.

The User Fee Goal Date is September 26, 1998

The Division Action Goal Date is September 1, 1998

Special Notes: The Division was informed by the firm last week, that natural disasters (i.e., flood and earthquake) had destroyed the plants and records in — — — — — sites on original memo). The sites listed above are the only ones available for audit, and are pivotal to approval.

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 20874/000
Stamp: 26-SEP-1997
Regulatory Due: 16-OCT-1999
Applicant: PHARMACIA AND UPJOHN
7000 PORTAGE RD
KALAMAZOO, MI 490010199
Priority: 4S
Org Code: 580

Action Goal:
District Goal: 27-MAY-1998
Brand Name: CYCLO-PROVERA CONTRACEPTIVE
INJ(ESTRADIO
Estab. Name:
Generic Name: ESTRADIOL
CYPIONATE/MEDROXYPROGESTERONE
Dosage Form: (SUSPENSION)
Strength: 5 MG/25 MG

Application Comment:

FDA Contacts: ID = 115760 , Project Manager
R. SEEVERS (HFD-120) 301-594-2850 , Review Chemist
M. RHEE (HFD-580) 301-827-4237 , Team Leader

Overall Recommendation: ACCEPTABLE on 10-NOV-1997 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: _____

DMF No: _____ AADA:
Responsibilities: _____
Profile: GSP OAI Status: NONE
Estab. Comment: _____ (on 29-OCT-1997
by R. SEEVERS (HFD-120) 301-594-2850)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-OCT-1997				DAMBROGIOJ
OC RECOMMENDATION	29-OCT-1997			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: 1810189
PHARMACIA AND UPJOHN CO
7000 PORTAGE ROAD
KALAMAZOO, MI 49001

DMF No: _____ AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment: THIS SITE MANUFACTURES BOTH DRUG SUBSTANCES. IT ALSO MANUFACTURES
THE DRUG PRODUCT FROM THE STERILIZED DRUG SUBSTANCES (on 29-OCT-
1997 by R. SEEVERS (HFD-120) 301-594-2850)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-OCT-1997				SEEVERSR
OC RECOMMENDATION	29-OCT-1997			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Profile: SVS OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-OCT-1997				DAMBROGIOJ
SUBMITTED TO DO	29-OCT-1997	10D			DAMBROGIOJ
DO RECOMMENDATION	07-NOV-1997			ACCEPTABLE BASED ON FILE REVIEW	MROBINSO

DET-DO COMPLETED A COMPREHENSIVE GMP INSPECTION OF PROFILE CLASS SVS

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

(STERILE FILLED SMALL VOLUME PARENTERALS) DATED 10/20-30/97. NO FDA-483 WAS
ISSUED AND THE REPORT WILL BE CLASSIFIED NAI.
OC RECOMMENDATION 10-NOV-1997 ACCEPTABLE DAMBROGIOJ
DISTRICT RECOMMENDATION

APPEARS THIS WAY
ON ORIGINAL

14-OCT-1999

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Page 1 of 2

Application: NDA 20874/000
Stamp: 26-SEP-1997
Regulatory Due: 16-OCT-1999
Applicant: PHARMACIA AND UPJOHN
7000 PORTAGE RD
KALAMAZOO, MI 490010199
Priority: 4S
Org Code: 580

Action Goal:
District Goal: 27-MAY-1998
Brand Name: ESTRADIO
Estab. Name:
Generic Name: ESTRADIOL
CYPIONATE/MEDROXYPROGESTERONE
Dosage Form: (SUSPENSION)
Strength: 5 MG/25 MG

Application Comment:

FDA Contacts: ID = 115760
R. SEEVERS (HFD-120) 301-594-2850, Project Manager
M. RHEE (HFD-580) 301-827-4237, Review Chemist
Team Leader

Overall Recommendation: ~~Not acceptable~~ on 14-OCT-1999 by S. FERGUSON (HFD-324) 301-827-0062
ACCEPTABLE on 10-NOV-1997 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment:

DMF No: AADA:
Responsibilities:
Profile: GSP OAI Status: NONE

Estab. Comment: THIS SITE STERILIZES BOTH OF THE DRUG SUBSTANCES (on 29-OCT-1997 by R. SEEVERS (HFD-120) 301-594-2850)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-OCT-1997				DAMBROGIOJ
OC RECOMMENDATION	29-OCT-1997			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: 1810189
PHARMACIA AND UPJOHN CO
7000 PORTAGE ROAD
KALAMAZOO, MI 49001

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE MANUFACTURER
Profile: CSN OAI Status: NONE

Estab. Comment: THIS SITE MANUFACTURES BOTH DRUG SUBSTANCES. IT ALSO MANUFACTURES THE DRUG PRODUCT FROM THE STERILIZED DRUG SUBSTANCES (on 29-OCT-1997 by R. SEEVERS (HFD-120) 301-594-2850)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-OCT-1997				SEEVERSR
OC RECOMMENDATION	29-OCT-1997			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Profile: SVS OAI Status: POTENTIAL OAI

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-OCT-1997				DAMBROGIOJ
SUBMITTED TO DO	29-OCT-1997	10D			DAMBROGIOJ
DO RECOMMENDATION	07-NOV-1997			ACCEPTABLE BASED ON FILE REVIEW	MROBINSO

14-OCT-1999

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Page 2 of 2

DET-DO COMPLETED A COMPREHENSIVE GMP INSPECTION OF PROFILE CLASS SVS
(STERILE FILLED SMALL VOLUME PARENTERALS) DATED 10/20-30/97. NO FDA-483 WAS
ISSUED AND THE REPORT WILL BE CLASSIFIED NAI.

OC RECOMMENDATION 10-NOV-1997

ACCEPTABLE DAMBROGIOJ
DISTRICT RECOMMENDATION
WITHHOLD FERGUSONS
EIR REVIEW-CONCUR
W/DISTRICT

OC RECOMMENDATION 14-OCT-1999

SIGNIFICANT GMP DEFICIENCIES

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 10/14/99 11:58:21 AM
From: Gurston Turner (TURNERG)
To: Jennifer Mercier (MERCIERJ)
Cc: George Prager (PRAGERG)
Cc: Bette Barton (BARTON)
Cc: Carol-Anne Currier (CURRIER)
Cc: Terri Rumble (RUMBLET)
Subject: final summary for NDA 20-874

MEMORANDUM
SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DEPARTMENT OF HEALTH AND HUMAN

FINAL SUMMARY OF CLINICAL INSPECTIONS

DATE: October 14, 1999

TO: J. Mercier, Regulatory Project Manager
Hixon, Clinical Reviewer
Division of Gynecologic and Urologic Drug Products, HFD-580

THROUGH: Bette Barton, PhD, MD
Chief, Good Clinical Practices Branch 1, HFD-46
Division of Scientific Investigations

FROM: G. Turner, PhD
Good Clinical Practices Branch 1, HFD-46
Division of Scientific Investigations

SUBJECT: Final Summary of Clinical Inspections

NDA: 20-874

APPLICANT: Pharmacia & Upjohn

DRUG: Lunelle (cycloprovera)

INDICATION(S): Injectable contraceptive

NAME IN ASSIGN INSPECT_D RECEIVED_ACTION_DA CLASS CROSS

KOVACS	18-JUL-98	24-AUG-98	PEND	VAI		
GALL	15-JUN-99		PEND	NAI		
MERRITT	15-JUN-99	28-JUN-99	02-SEP-99	21-SEP-99	NAI	09869
DUNSTON	15-JUN-99	09-AUG-99	01-SEP-99	21-SEP-99	NAI	09866

1. [] M.D.

Protocol # M/5415/004

42 subjects were entered into the study. 6 of the records from the study

APPEARS THIS WAY
ON ORIGINAL

subjects were audited. No problems were found. Based on this audit DSI recommends that the study be used in support of the NDA.

Site of [redacted]

protocol # M/5415/0004

The inspection was done on the records of 20/40 subjects entered into the study at this site. Based on a review of the EIR, DSI recommends that the study be used in support of the NDA. No discrepancies were found when a comparison of the data in the CRF's was compared to raw supporting data.

3. Site of [redacted]

Protocol #M5415-004

The audit for this site was initiated on September 7, 1999. The field investigator audited the records of 10 subject from a study population of 483 subjects. No problems were found and DSI recommends that the study be used in support of the NDA. This recommendation is based on a draft copy of the EIR.

4. Site of [redacted]

subjects were entered into the study and an audit was done on all of records for the subjects. Due to the age of the study many of the supporting documentation was not maintained. In addition there were 16 of 143 ineligible subjects. This ineligibility was due to a lack of required duration of normal menstrual cycles and lack of histories of normal menstrual cycles. Despite the missing documentation, DSI recommends that the study be used in support of the NDA

RECOMMENDATION

DSI recommends that the data from these studies be used to support drug claims.

Follow-up action is not indicated.

- cc:
- NDA #20-874
- HFD-45 Division File
- HFD-46 Prager
- HFD-46 Barton
- HFD-46 CIB File
- HFD-46 Reading File

**APPEARS THIS WAY
ON ORIGINAL**

MODE = MEMORY TRANSMISSION

START-OCT-15 15:19 END-OCT-15 15:20

FILE NO. =411

STN NO.	COMM.	ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK		916168338409	002/002	00:00:51

LTA FAX

-FDA/DRUDP

***** -FDA/DRUDP - ***** 301 827 4267- *****



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-874

OCT 15 1999

Pharmacia & Upjohn
Attention: P.K. Narang, Ph.D., F.C.P.
Liaison Director, Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 49001

Dear Dr. Narang:

Please refer to your new drug application (NDA) dated September 25, 1997, received September 26, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LUNELLE™ Monthly Contraceptive Injection (medroxyprogesterone acetate and estradiol cypionate injectable suspension).

We acknowledge receipt of your submissions dated April 15 and 27, August 6, 18, 20, 25, 26, and 31, September 1, 3, 7 and 27, and October 12, 13 and 15, 1999. Your submission of April 15, 1999, constituted a complete response to our September 25, 1998, action letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the inspector. Satisfactory resolution of these deficiencies will be required before this application may be approved.

In addition, it will be necessary for you to submit draft labeling. The labeling should be revised as in the enclosed marked-up draft.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

As discussed on October 12, 1999, and subsequently agreed by you via October 15, 1999, facsimile, the Division requests that you develop and execute further clinical trials to determine the added benefit of the estrogen-component of this combination product. Studies would include a comparison of bone mineral density changes, ovulation rates and alterations in bleeding patterns between LUNELLE™ Monthly Contraceptive Injection and your medroxyprogesterone acetate alone product.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those

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MODE = MEMORY TRANSMISSION

START=OCT-15 15:21

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FILE NO.-412

STN NO.	COMM.	ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	#	916168338489	040/040	00:20:38

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***** -FDA/DRUDP - ***** 301 827 4267- *****

LUNELLE™ Monthly Contraceptive Injection
(medroxyprogesterone acetate and estradiol cypionate injectable suspension)
Amended Proposed Package Insert

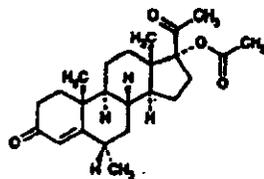
October 15, 1999 - FDA Version

LUNELLE™ Monthly Contraceptive Injection
medroxyprogesterone acetate and estradiol cypionate injectable suspension

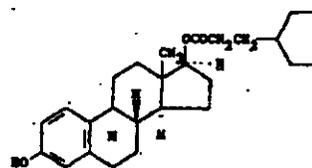
Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

DESCRIPTION

LUNELLE™ Monthly Contraceptive Injection contains medroxyprogesterone acetate and estradiol cypionate as its active ingredients. The chemical name for medroxyprogesterone acetate is pregn-4-ene-3,20-dione,17-(acetyloxy)-6-methyl-,(6α)-. The empirical formula is C₂₄H₃₄O₄ and its molecular weight is 386.53. Medroxyprogesterone acetate is a white to off-white, odorless crystalline powder that is stable in air and melts between 200°C and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in alcohol and methanol, slightly soluble in ether, and practically insoluble in water. The chemical name for estradiol cypionate is estra-1,3,5,(10)-triene-3,17-diol,(17β)-,17-cyclopentanepropanoate. Estradiol cypionate is a white to off-white crystalline powder that melts between 149°C and 153°C. It is soluble in alcohol, acetone, chloroform, and dioxane; sparingly soluble in vegetable oils; and practically insoluble in water. The empirical formula is C₂₈H₃₆O₃ and its molecular weight is 396.57. The structural formulas for these ingredients are represented below:



Medroxyprogesterone Acetate



Estradiol Cypionate

LUNELLE™ Monthly Contraceptive Injection is available as a 0.5 mL aqueous suspension and contains 25 mg medroxyprogesterone acetate and 5 mg estradiol cypionate. Inactive ingredients are 0.9 mg methylparaben, 14.28 mg polyethylene glycol, 0.95 mg polysorbate 80, 0.1 mg propylparaben, 4.28 mg sodium chloride, and sterile water for injection.

FDA: Please contact the manufacturer in writing above the complete response submission.

BEST POSSIBLE COPY

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Attn: Eufrecina Deguia



Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

May 22, 2000

Dr. Susan Allen, Acting Director
Division of Reproductive and Urological Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 20-874
Lunelle Monthly Contraceptive Injection
(Medroxyprogesterone Acetate and
Estradiol Cypionate Injection)

General Correspondence
Updated Composition Pages

Dear Dr. Allen:

In response to a May 17, 2000 request by Dr. David Lin (FDA- Chemistry Reviewer), Pharmacia and Upjohn is pleased to submit an updated Composition Section for the above referenced product.

The manufacturing of Lunelle Monthly Contraceptive Injection is a two-stage process. Initially, a sterile vehicle containing the "other ingredients" is prepared (Part I). Then, this vehicle is used to manufacture the finished product (Part II). Due to manufacturing loss during Part I and further dilution occurring in Part II, the concentration of the "other ingredients" in the sterile vehicle is different from that in the finished product. Therefore, as requested, we are updating the Composition Section of the NDA. The attached updated pages identify the amount per ml and representative batch formulas of each ingredient in both the sterile vehicle and the finished product.

Should there be any questions regarding this submission, please call me at 616-833-9896.
Send all correspondence to 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY



P.K. Narang, Ph.D., F.C.P.
Liaison Director
Global Regulatory Affairs

PKN:kmv
Attachment

cc: EuFrecina Deguia (Consumer Safety Officer)
Copy of the letter+356H
Dr. David Lin

APPEARS THIS WAY
ON ORIGINAL

NDA 20-874

Lunelle™ Monthly Contraceptive Injection
(medroxyprogesterone acetate and estradiol cypionate)

Pharmacia & Upjohn
4S

PM: Jennifer Mercier

Phone: 7-4260

HFD-580

Submission Date: April 7, 2000
User Fee Goal Date: October 7, 2000

Chemistry Section

APPEARS THIS WAY
ON ORIGINAL

5
REC-
10/11/00
8:32A17

SUPPORTING DOCUMENTS:

See Chem. Rev. #1 #2, and #3, and memorandum for this NDA.

RELATED DOCUMENTS:

N/A

CONSULTS:

See Chem. Rev. #1 #2, and #3, and memorandum for this NDA.

The proposed name, Lunelle™ Monthly Contraceptive Injection, was submitted to the LNC on April 9, 1999, and found to be acceptable on June 6, 1999.

REMARKS/COMMENTS:

The sponsor submitted a proposed trademark, Lunelle, to replace _____ Lunelle was found to be acceptable by the LNC. However, in the February 24, 1999 amendment, the sponsor requested that the noun " _____ " be included with Lunelle as the trademark. The sponsor's request was formally submitted to the LNC on April 9, 1999, along with the following alternatives, 1) _____, 2) Lunelle Monthly Contraceptive Injection, and 3) _____ (see April 12, 1999 amendment). The LNC determined all four requested trademarks to be acceptable (see Appendix A). Therefore, the sponsor has chosen to use "Lunelle Monthly Contraceptive Injection".

In the August 26, 1999 general correspondence, the sponsor has requested approval of a correction to the NDA. In the NDA the drug product specification for the impurity " _____ " is NMT (_____). However, in DMF _____ for medroxyprogesterone acetate drug substance this same impurity has a limit of NMT _____. This DMF was specifically reviewed for the proposed impurities specifications and found to be acceptable (see Chem. Rev. #8 dated March 5, 1997 by Dr. Bob SeEVERS). The sponsor has submitted data for 40 lots of bulk drug substance and 1 lot of bulk drug substance used in the manufacture of the clinical study batch of drug product. The data does support a limit of _____ for the _____ in the DMF). To be consistent the proposal for a _____ impurity specification of NMT _____ in the drug product is acceptable.

The final review of the labeling will be presented in a memorandum.

The April 12, 1999 amendment contains the request for tradename review.

The September 3, 1999 amendment contains batch data information on the MPA drug substance lot used in the drug product clinical lots.

Summary of Chemistry Review**A. Drug Substance:**

1. **Description & Characterization:** Satisfactory. See Chem. Rev. #1.
2. **Manufacturers:** Satisfactory. See Chem. Rev. #1.
3. **Synthesis:** Satisfactory. See Chem. Rev. #1.
4. **Process Controls:** Satisfactory. See Chem. Rev. #1.
5. **Reference Standard:** Satisfactory. See Chem. Rev. #1.
6. **Specifications/Methods:** Satisfactory. See Chem. Rev. #1.
7. **Container:** Satisfactory. See Chem. Rev. #1.
8. **Stability:** Satisfactory. See Chem. Rev. #1.

B. Drug Product:

- 1/2. **Components/Composition:** Satisfactory. See Chem. Rev. #1.
3. **Specifications/Methods for Drug Product Components:** Satisfactory. See Chem. Rev. #1.
4. **Manufacturer:** Satisfactory. See Chem. Rev. #1.
5. **Methods of Manufacturing:** Satisfactory. See Chem. Rev. #2.
6. **Regulatory Specifications/Methods:** Satisfactory. See Chem. Rev. #2 and #5.
7. **Container/Closure System:** Satisfactory. See Chem. Rev. #1.
8. **Microbiology:** Satisfactory. See Micro Rev. (05-MAR-1998).
9. **Stability:** Satisfactory. See Chem. Rev. #1.

C. **Investigational Formulations:** Satisfactory. See Chem. Rev. #1.

D. **Environmental Assessment:** Satisfactory. See Chem. Rev. #1.

E. **Methods Validation:** *Pending*. The complete methods validation package will be submitted to FDA labs.

F. **Labeling:** *Pending*. See Chem. Rev. #3 and #5.

G. **Establishment Inspection:** Satisfactory. See Chem. Rev. #1.

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	11845	HFDE	580	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
ATTENTION:	David T. Lin	Lunelle Monthly Contraceptive Injection		medroxyprogesterone acetate and estradiol cypionate injection	

A. Look-alike/Sound-alike

Potential for confusion:

Low	Medium	High

B. Misleading Aspects:

C. Other Concerns:

Cannot have dosing info in reminder ads

D. Established Name

Satisfactory
 Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

XXX ACCEPTABLE
with concerns

UNACCEPTABLE

F. Signature of Chair/Date

|S|

6/7/99

SUPPORTING DOCUMENTS:

See Chem. Rev. #1 and #2 for this NDA.

RELATED DOCUMENTS:

N/A

CONSULTS:

See Chem. Rev. #1 and #2 for this NDA.

The proposed name, _____ was submitted to the LNC on June 30, 1998, and found to be acceptable on September 3, 1998.

REMARKS/COMMENTS:

The proposed trademark, _____ was found to be acceptable by the LNC. However, in the August 7, 1998 amendment, the sponsor requests withdrawal of the proposed trademark. Until another proposed trademark is submitted by the sponsor, the recommended trademark will be _____

APPEARS THIS WAY
ON ORIGINAL