

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-874

CHEMISTRY REVIEW(S)

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

NDA #: 20-874

CHEMISTRY REVIEW #: 7 (addendum #1)

DATE REVIEWED: 04-OCT-2000

| <u>SUBMISSION TYPE</u> | <u>DOCUMENT DATE</u> | <u>CDER DATE</u> | <u>ASSIGNED DATE</u> |
|------------------------|----------------------|------------------|----------------------|
| Original | 26-SEP-97 | 29-SEP-97 | 06-OCT-97 |
| Amendment | 12-SEP-00 | 14-SEP-00 | |

NAME & ADDRESS OF SPONSOR: Pharmacia & Upjohn Company
7000 Portage Road
Kalamazoo, MI 49001-0199

OCT 4 2000

DRUG PRODUCT NAME:

Proprietary: Lunelle Monthly Contraceptive Injection
Nonproprietary/Established/USAN: Medroxyprogesterone acetate and Estradiol cypionate Injectable Suspension

Code Name/#:
Chem.Type/Ther.Class: 3S

PHARMACOLOGICAL CATEGORY/INDICATION: Prevention of pregnancy

DOSAGE FORM: Suspension for injection
STRENGTHS: 25 mg medroxyprogesterone acetate/5 mg estradiol cypionate in 0.5 mL aqueous suspension

ROUTE OF ADMINISTRATION: Intra-muscular

DISPENSED: Rx OTC

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

- 1) Medroxyprogesterone acetate: see USP
- 2) Estradiol cypionate: see USP

CONCLUSIONS & RECOMMENDATIONS:

This NDA may be approved from a CMC point of view.

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

/S/

10/4/00

R/D Init by: *LS*
filename: nda20874ad.7 (doc)

David T. Lin, Ph.D.
Review Chemist

APPEARS THIS WAY
ON ORIGINAL

OCT 4 2000

Summary of Chemistry Review of NDA 20-874

A. Drug Substances:

Medroxyprogesterone acetate is a synthetic derivative of natural progesterone and manufactured by Pharmacia & Upjohn (DMF _____) in compliance to cGMP. **Estradiol cypionate** is also synthetic derivative of natural estradiol and manufactured by Pharmacia & Upjohn in compliance to cGMP (DMF _____)

Both drug substances were sterilized with _____, by _____ and the facility is deemed in compliance to cGMP.

Both drug substances are listed in USP 24.

B. Drug Product:

The drug product is an injectable (IM) sterile suspension for the prevention of pregnancy. It is a combination of medroxyprogesterone (25mg) and estradiol cypionate (5mg) suspended in aqueous vehicle (0.5ml) containing polysorbate _____, polyethylene glycol _____, sodium chloride _____, methylparaben _____, and propylparaben _____. It is packed in a _____ with a _____

The drug product is manufactured by Pharmacia & Upjohn and its facility is deemed in compliance to cGMP.

The quality of the drug product is controlled by the specifications such as appearance, assays for medroxyprogesterone acetate and estradiol cypionate, content uniformity for each drug substance, identification, degradation products, pH, sterility, volume of injection, endotoxin, particle size, and specific gravity. The proposed specification including for each test is deemed adequate. Sterility assurance is deemed adequate from the microbiologist's point of view.

The drug product is packaged in _____ manufactured by _____ (DMF _____ with a _____ having _____ The _____ is manufactured by _____, in _____ (DMF _____)

All the packaging components are considered to be adequate to protect the drug product during the shelf life.

Based on 18-month real time _____ data from _____ production scale batches, 18-month expiry date is granted.

The firm proposed a shelf life specification for pH _____ which is different from the release specification _____. This is considered to be acceptable based on the fact that two drug products, Depo-Provera (NDA 12-541) and Depo-Provera Contraceptive Injection (20-246) also have similar pH ranges _____ during the shelf life.

The tradename, Lunelle Monthly Contraceptive injection, was accepted by OPDRA on May 11, 2000. Description and How supplied sections of the labeling are also deemed satisfactory.

C. Conclusion and Recommendation:

From the chemistry, manufacturing and controls point of view, as recommended by the primary reviewer, this NDA may be approved.

/S/

10/4/00

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader
For the Division of Reproductive and Urologic Drug Products
DNDC II, Office of New Drug Chemistry

cc: original NDA 20-874
HFD-580/Div File
HFD-580/DLin/Mrhee/JMercier
HFD-820/JGibbs/SKoepe

APPEARS THIS WAY
ON ORIGINAL

Yuan-Yuan & Chuck,

Another action package—this one is for Lunelle (NDA 20-874). This is the third review cycle (it had an NA the first time and an AE the second) and the division is recommending approval. The due date is October 7. In addition to the CMC information, in the inside cover you'll find copies of:

1. October 15, 1999 AE letter
2. package insert text
3. immediate container and carton labels
4. trade name review
5. Division Director's summary memo.

|S|

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ON ORIGINAL

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

151
MAY 23 2000

NDA #: 20-874

CHEMISTRY REVIEW #: 7

DATE REVIEWED: 23-MAY-2000

| <u>SUBMISSION TYPE</u> | <u>DOCUMENT DATE</u> | <u>CDER DATE</u> | <u>ASSIGNED DATE</u> |
|------------------------|----------------------|------------------|----------------------|
| Original | 26-SEP-97 | 29-SEP-97 | 06-OCT-97 |
| Amendment | 06-APR-00 | 07-APR-00 | 11-APR-00 |
| Amendment | 22-MAY-00 | 23-MAY-00 | 23-MAY-00 |

NAME & ADDRESS OF SPONSOR: Pharmacia & Upjohn Company
7000 Portage Road
Kalamazoo, MI 49001-0199

DRUG PRODUCT NAME:

Proprietary: Lunelle Monthly Contraceptive Injection
Nonproprietary/Established/USAN: Medroxyprogesterone acetate and Estradiol cypionate Injectable Suspension

Code Name/#:
Chem. Type/Ther. Class: 3S

PHARMACOLOGICAL CATEGORY/INDICATION: Prevention of pregnancy

DOSAGE FORM: Suspension for injection
STRENGTHS: 25 mg medroxyprogesterone acetate/5 mg estradiol cypionate in 0.5 mL aqueous suspension

ROUTE OF ADMINISTRATION: Intra-muscular

DISPENSED: Rx OTC

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

- 1) Medroxyprogesterone acetate: see USP
- 2) Estradiol cypionate: see USP

CONCLUSIONS & RECOMMENDATIONS:

This NDA may be approved from a CMC point of view.

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

R/D Init by:
filename: nda20874.7 (doc)

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5/23/00

David T. Lin, Ph.D.
Review Chemist

151
5/23/00

APPEARS THIS WAY
ON ORIGINAL

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

SEP 22 1999

NDA #: 20-874

CHEMISTRY REVIEW #: 4

DATE REVIEWED: 20-SEP-99

| <u>SUBMISSION TYPE</u> | <u>DOCUMENT DATE</u> | <u>CDER DATE</u> | <u>ASSIGNED DATE</u> |
|------------------------|----------------------|------------------|----------------------|
| Original | 26-SEP-97 | 29-SEP-97 | 06-OCT-97 |
| Amendment | 12-APR-99 | 12-APR-99 | |
| General Corres. | 26-AUG-99 | 27-AUG-99 | |
| Amendment | 03-SEP-99 | 08-SEP-99 | |

NAME & ADDRESS OF SPONSOR:

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

DRUG PRODUCT NAME:

Proprietary: Lunelle™ Monthly Contraceptive Injection
Nonproprietary/Established/USAN: Medroxyprogesterone acetate and Estradiol cypionate
Code Name/#:
Chem. Type/Ther. Class: 3S

PHARMACOLOGICAL CATEGORY/INDICATION: Prevention of pregnancy

DOSAGE FORM:

Suspension for injection

STRENGTHS:

25 mg medroxyprogesterone acetate/5 mg estradiol cypionate in 0.5 mL aqueous suspension

ROUTE OF ADMINISTRATION:

Intra-muscular

DISPENSED:

Rx OTC

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

1) Medroxyprogesterone acetate: see USP

2) Estradiol cypionate: see USP

CONCLUSIONS & RECOMMENDATIONS:

This review covers the issue of the proposed trademark and revised drug product specifications. This NDA is approvable pending final labeling review.

cc:

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

R/D Init by: *151 9/22/99*
filename: nda20874.5 (doc)

/S/
9/22/99
David T. Lin, Ph.D.
Review Chemist

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

NDA #: 20-874

CHEMISTRY REVIEW #: 3

DATE REVIEWED: 04-SEP-98

| <u>SUBMISSION TYPE</u> | <u>DOCUMENT DATE</u> | <u>CDER DATE</u> | <u>ASSIGNED DATE</u> |
|------------------------|----------------------|------------------|----------------------|
| Original | 26-SEP-97 | 29-SEP-97 | 06-OCT-97 |
| Amendment | 07-AUG-98 | 12-AUG-98 | |

NAME & ADDRESS OF SPONSOR:

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

DRUG PRODUCT NAME:

Proprietary: Cyclo-Provera Injection
Nonproprietary/Established/USAN: Medroxyprogesterone acetate and Estradiol cypionate
Code Name/#:
Chem. Type/Ther. Class: 3S

PHARMACOLOGICAL CATEGORY/INDICATION: Prevention of pregnancy

DOSAGE FORM:

Suspension for injection

STRENGTHS:

25 mg medroxyprogesterone acetate/5 mg estradiol cypionate in 0.5 mL aqueous suspension

ROUTE OF ADMINISTRATION:

Intra-muscular

DISPENSED:

 x Rx OTC

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

- 1) Medroxyprogesterone acetate: see USP
- 2) Estradiol cypionate: see USP

CONCLUSIONS & RECOMMENDATIONS:

This review covers the pending issue of the proposed trademark. This NDA can now be approved.

cc:

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

R/D Init by: *151 9/4/98*
filename: nda208.4.9 (doc)

/S/

9/4/98

David T. Lin, Ph.D.
Review Chemist

APPEARS THIS WAY
ON ORIGINAL

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

151
JUL - 7 1998

NDA #: 20-874

CHEMISTRY REVIEW #: 2

DATE REVIEWED: 07-JUL-98

| <u>SUBMISSION TYPE</u> | <u>DOCUMENT DATE</u> | <u>CDER DATE</u> | <u>ASSIGNED DATE</u> |
|------------------------|----------------------|------------------|----------------------|
| Original | 26-SEP-97 | 29-SEP-97 | 06-OCT-97 |
| Amendment | 21-MAY-98 | 22-MAY-98 | 27-MAY-98 |
| Amendment | 29-JUN-1998 | | 30-JUN-1998 |

NAME & ADDRESS OF SPONSOR:

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

DRUG PRODUCT NAME:

Proprietary: Cyclo-Provera Injection
Nonproprietary/Established/USAN: Medroxyprogesterone acetate and Estradiol cypionate
Code Name/#: -
Chem. Type/Ther. Class: 3S

PHARMACOLOGICAL CATEGORY/INDICATION: Prevention of pregnancy

DOSAGE FORM:

Suspension for injection

STRENGTHS:

25 mg medroxyprogesterone acetate/5 mg estradiol cypionate in 0.5 mL aqueous suspension

ROUTE OF ADMINISTRATION:

Intra-muscular

DISPENSED:

 x Rx OTC

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

1) Medroxyprogesterone acetate: see USP

2) Estradiol cypionate: see USP

CONCLUSIONS & RECOMMENDATIONS:

This review covers the response to the deficiencies documented in Chem. Rev. #1. This NDA is now approvable pending an acceptable recommendation of the trademark by the Labeling and Nomenclature Committee.

cc:

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

R/D Init by:

filename: nda20874.2 (doc)

151
David T. Lin, Ph.D.
Review Chemist

7/7/98

APPEARS THIS WAY
ON ORIGINAL

5
APR 21 1998

**DIVISION OF REPRODUCTIVE AND UROLOGIC
DRUG PRODUCTS HFD-580**

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-874 CHEM.REVIEW #: 1 REVIEW DATE: 13-MAR-98 REVISED: 15-APR-1998

| <u>SUBMISSION TYPE</u> | <u>DOCUMENT DATE</u> | <u>CDER DATE</u> | <u>ASSIGNED DATE</u> |
|------------------------|----------------------|------------------|----------------------|
| Original NDA N-000 | 26-SEP-1997 | 29-SEP-1997 | 06-OCT-1997 |

NAME & ADDRESS OF APPLICANT:

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

DRUG PRODUCT NAME

Proprietary: *

Nonproprietary/USAN:

Code Name/#:

Chem. Type/Ther. Class:

Cyclo-Provera™ Injection

Medroxyprogesterone acetate and Estradiol
cypionate

3S

PATENT STATUS:

NA

PHARMACOL.CATEGORY/INDICATION:

Prevention of pregnancy

DOSAGE FORM:

suspension for injection

STRENGTHS:

25 mg medroxyprogesterone acetate/5mg
estradiol cypionate in 0.5 mL aqueous
suspension.

ROUTE OF ADMINISTRATION:

Intra-muscular

DISPENSED: *

Rx OTC

SPECIAL PRODUCTS:

Yes No

(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

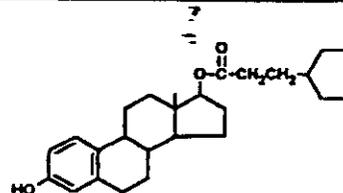
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Estradiol cypionate

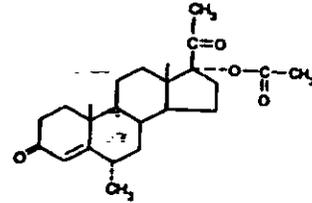
Estra-1,3,5(10)-triene-3,17βdiol, 17-cyclopentylpropionate

C₂₆H₃₆O₃

M.W. = 396.57



Medroxyprogesterone acetate
 Pregn-4-en-3,20-dione,17-(acetyloxy)-6-methyl-, (6α)
 $C_{24}H_{34}O_4$
 M.W. = 386.53



SUPPORTING DOCUMENTS:

| Type/Number | Subject | Holder | Status | Review Date | Letter Date |
|-------------|-----------------------------|--------------------|------------|-------------|-------------|
| _____ | Medroxyprogesterone acetate | Pharmacia & Upjohn | Acceptable | 3/5/98 | |
| _____ | Estradiol cypionate | Pharmacia & Upjohn | Acceptable | 3/5/98 | |
| _____ | _____ | _____ | Acceptable | 7/15/97 | |
| _____ | _____ | _____ | Acceptable | 3/11/98 | |

CONSULTS:

An Establishment Evaluation Request was filed for the manufacturing sites for this application on October 29, 1997 and returned as Acceptable on November 10, 1997. The proposed name, Cyclo-Provera, was submitted to the Labeling and Nomenclature Committee on October 29, 1997 and returned as Unacceptable on February 23, 1998. The reason for this finding is that the proposed name is in conflict with 21 CFR 201.6(b) because it is a combination drug and the name includes or suggests the name of one or more but not all ingredients; i.e. Provera suggests medroxyprogesterone acetate, but there is no indication in the proposed name of the estrogenic component. The sponsor was informed of this on February 25, 1998 and requested to submit a new name for drug product. A Microbiology consult was sent on March 19, 1998.

REMARKS/COMMENTS:

This NDA is for drug product that is a combination of medroxyprogesterone acetate and estradiol cypionate in an injectable suspension for the prevention of pregnancy.

CONCLUSIONS & RECOMMENDATIONS:

The application may be approved from a chemistry standpoint when the sponsor has satisfactorily addressed the following issues:

- The sponsor needs to indicate whether it plans to perform any reprocessing operations on the drug product if it does not meet release specifications.
- There is a discrepancy between the relative response factors submitted for the MPA analog in the _____ assay. The sponsor needs to clear this up.

BEST POSSIBLE COPY

- The pH specification proposed for the drug product of _____ at expiry is different from the pH range approved for other sterile medroxyprogesterone acetate suspensions which is _____. The latter range is also provided for in the USP monograph for Sterile Medroxyprogesterone Acetate Suspension. The sponsor should revise the pH range for this drug product to _____.
- The pH of the drug product decreases over time in the stability studies. The sponsor should be asked to comment on a possible mechanism for this observation.
- The sponsor needs to address the apparent manufacturing overage for both of the drug substances.
- The proposed name for the drug product, Cyclo-Provera, is not acceptable as noted above under Consults. The sponsor needs to submit an acceptable name for the drug product.

Please see Section H of this review: Draft Deficiency Letter.

cc:

Orig. NDA 20-874

HFD-580/Division File

HFD-580/Chemist/Seevers/Rhee

HFD-580/CSO/Kish

R/D Init by: Rhee

4/21/98

IS/

IS/

4/25/98

Robert H. Seevers, Chemist

APPEARS THIS WAY
ON ORIGINAL

19 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

14 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling