

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**75951**

**CHEMISTRY REVIEW(S)**

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 75-951

FIRM: Barr Laboratories, Inc.  
2 Quaker Road  
P. O. Box 2900  
Pomona, NY 10970

DOSAGE FORM: Tablets

STRENGTH: 5 mg

DRUG: Norethindrone Acetate Tablets USP

CGMP STATEMENT/EIR UPDATED STATUS:  
EER for all facilities is acceptable on 10-2-00.

BIO STUDY:  
Bio status: Acceptable as of 11-30-00.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):  
MV is not required.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?  
Containers used in the stability studies are identical to those listed in container section.

LABELING:  
Acceptable for approval per A. Payne's review completed on 4-17-01.

STERILIZATION VALIDATION (IF APPLICABLE):  
N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.):  
Lot # 1021110001R: Size: ( ) kg ( ) Tablets.

Source of NDS:  
DMF # ( ): Adequate per review completed on 1-31-01 by this reviewer.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)  
Stability batch is:

Lot # 1021110001R: ( ) kg ( ) Tablets)

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?  
Intended production batch size: ( ) kg ( ) Tablets).

Manufacturing process for the intended production size is identical to that used for the exhibit/bio/stability batch.

Mujahid L. Shaikh/4/18/01  
Review Chemist  
Division of Chemistry I  
OGD/CDER  
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HFD-625/MSmela/4/18/01  
F/T by: DJ 4/18/01

( /S/ 4/18/01 )

( /S/ 4/18/01 )

FEB 8 2001

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-951 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Norethindrone Acetate Tablets, 5 mg

The deficiencies presented below represent FAX deficiencies.

A. Deficiencies:

1. We have the following comments regarding the drug substance:
  - a. Please revise your residual limits to be identical to those of
  - b. Please examine if the drug substance may exhibit Please establish a control based on the material used in the biobatch, if appropriate.
2. We have the following comments regarding the drug product controls:
  - a. Your proposed ranges for (in-process weight, hardness and thickness) are very loose. Narrower ranges are requested based on your available data.
  - b. Please revise your (in-process testing based on the proposal submitted to ANDA 75-478 on January 12, 2001.
3. Please include all impurities associated with the drug substance in release and stability testing of the drug product except for specific individual impurities that are proven with data not to be degradants.
4. Please clarify your use of bulk packaging. Is it for in-house use or sale to repackagers?

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please submit additional long term stability data for the exhibit batch, if available.
2. Please acknowledge that the USP monograph methods are the regulatory methods and shall rule in the event of a dispute.
3. Labeling deficiencies will also need to be addressed in your reply.

4. A satisfactory compliance evaluation is necessary for approval and we have requested an evaluation from the Office of Compliance.

Sincerely yours,

/S/

Rashmikant M. Patel, Ph.D.  
Director  
Division of Chemistry I  
Office of Generic Drugs  
Center for Drug Evaluation and Research

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-951

3. NAME AND ADDRESS OF APPLICANT

Barr Laboratories  
2 Quaker Road  
P. O. Box 2900  
Pomona, NY 10970

4. LEGAL BASIS FOR SUBMISSION

Reference Listed Drug Product: Aygestin® (Norethindrone Acetate Tablets) (Wyeth Ayerst NDA # 18-405).

Barr certified that there are no patents that claim the listed drug referred to in this application or claim a use of the listed drug. Patent information has not been filed with the FDA

The indications the proposed drug product is going to be used for, active ingredient, route of administration, dosage form, strength and labeling is same as listed drug product.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

None used.

7. NONPROPRIETARY NAME

Norethindrone Acetate Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

FIRM:

Original submission: 8-25-00

NC: 9-15-00

NC: 9-22-00 (ESD)

FDA:

Accepted for filing on: 8-28-00 (Acknowledgement letter: 9-25-00)

10. PHARMACOLOGICAL CATEGORY

For treatment of secondary amenorrhea, endometriosis, abnormal uterine bleeding due to hormonal imbalance.

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF  
DMF  
DMF  
DMF  
DMF

DMF ✓  
DMF  
DMF  
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DMF  
DMF  
DMF  
DMF  
DMF

13. DOSAGE FORM  
Tablets

14. POTENCY  
5 mg

15. CHEMICAL NAME AND STRUCTURE:

Chemical Name for Norethindrone Acetate: See USP 24, page 1197

CAS #: [68-22-4]

Structure: See USP 24, page 1197

16. RECORDS AND REPORTS  
N/A

17. COMMENTS

A. General Comments:

1. Composition for the drug product is acceptable.
2. Referenced DMF for Norethindrone is found adequate per review completed on 1-31-01 by this reviewer.
3. Barr packaged the entire exhibit batches into proposed packaging configurations with 50 count.
4. Drug product is a USP material; therefore, samples for MV will not be required
5. Labeling review is deficient.
6. Bio Review acceptable.

B. Comments to be included in NA letter:

All the comments listed in section # 23, 28, 29, and 32.

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approved. A NA letter with FAX amendment is being faxed to the firm including all the deficiencies identified in this review.

19. REVIEWER:

Mujahid L. Shaikh

DATE COMPLETED:

1-17-01

Revised on 1-30-01 to include Mike Smela's comments  
Revised on 2-5-01 to include Mike Smela's comments.

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commercial

information

Chem Review #1

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-951 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Norethindrone Acetate Tablets, 5 mg

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A. Deficiencies:

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  - a. Please revise your residual limits to be identical to those of
  - b. Please examine if the drug substance may exhibit Please establish a control based on the material used in the biobatch, if appropriate.
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  - a. Your proposed ranges for in-process weight, hardness and thickness are very loose. Narrower ranges are requested based on your available data.
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3. Labeling deficiencies will also need to be addressed in your reply.

4. A satisfactory compliance evaluation is necessary for approval and we have requested an evaluation from the Office of Compliance.

Sincerely yours,

 /S/

Rashmikant M. Patel, Ph.D.  
Director  
Division of Chemistry I  
Office of Generic Drugs  
Center for Drug Evaluation and Research

*Chemistry Closed*

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-951

3. NAME AND ADDRESS OF APPLICANT

Barr Laboratories  
2 Quaker Road  
P. O. Box 2900  
Pomona, NY 10970

4. LEGAL BASIS FOR SUBMISSION

Reference Listed Drug Product: Aygestin® (Norethindrone Acetate Tablets) (Wyeth Ayerst NDA # 18-405).

Barr certified that there are no patents that claim the listed drug referred to in this application or claim a use of the listed drug. Patent information has not been filed with the FDA

The indications the proposed drug product is going to be used for, active ingredient, route of administration, dosage form, strength and labeling is same as listed drug product.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

None used.

7. NONPROPRIETARY NAME

Norethindrone Acetate Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

FIRM:

Original submission: 8-25-00

NC: 9-15-00

NC: 9-22-00 (BIO)

\* Minor Amendment: 3-9-01 (Response to NA letter dated 2-8-01)

\* Labeling Amendment: 3-12-01

FDA:

Accepted for filing on: 8-28-00 (Acknowledgement letter: 9-25-00)

NA letter: 2-8-01

10. PHARMACOLOGICAL CATEGORY

For treatment of secondary amenorrhea, endometriosis, abnormal uterine bleeding due to hormonal imbalance.

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF /  
DMF L

DMF  
DMF

13. DOSAGE FORM  
Tablets

14. POTENCY  
5 mg

15. CHEMICAL NAME AND STRUCTURE:

Chemical Name for Norethindrone Acetate: See USP 24, page 1197

CAS #: [68-22-4]

Structure: See USP 24, page 1197

16. RECORDS AND REPORTS  
N/A

16. COMMENTS

1. Referenced DMF ( ) for Norethindrone is found adequate per review completed on 1-31-01 by this reviewer.
2. Drug product is a USP material; therefore, samples for MV will not be required
3. Labeling response is pending review.
4. Bio Review acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS

Chemistry Closed.

FPL review is pending.

19. REVIEWER:  
Mujahid L. Shaikh

DATE COMPLETED:  
4-3-01  
Revised on 4-10-01

*Labeling acceptable  
Per Payne/Grace on  
4/17/01  
H. Shaikh  
4/18/01*

cc: AND 75-951  
DUP File  
Division File  
Field Copy

Endorsements:

HFD-625/M. Shaikh/ ( )  
HFD-625/M. Smela/

F/T by:

*IS/ 4/10/01*  
*( IS/ 4/10/01*

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*Chem Review #2*