

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
75951

CORRESPONDENCE

ANDA 75-951

Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970
|||||

SEP 21 2000

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated September 15, 2000 and your correspondence dated September 15, 2000.

NAME OF DRUG: Norethindrone Acetate Tablets, USP, 5 mg

DATE OF APPLICATION: August 25, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: August 28, 2000

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Michelle Dillahunt
Project Manager
(301) 827-5848

Sincerely yours,

MSI
HH
Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

September 22, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NEW CORRESP
NC/Bio

REFERENCE: ANDA 75-951
AMENDMENT TO PENDING ANDA
NORETHINDRONE ACETATE TABLETS, USP 5 MG
ELECTRONIC SUBMISSION OF CMC AND BA/BE

Reference is made to our Abbreviated New Drug Application submitted August 25, 2000 under 505(j) of the Federal Food, Drug and Cosmetic Act for Norethindrone Acetate Tablets, USP 5 mg.

As indicated in our original application, Barr Laboratories, Inc. is amending the above referenced application to provide the CMC and BA/BE electronic submission. The CMC and BA/BE electronic submissions are contained on separate diskettes labeled " CMC ESD & Companion Document" and "BA/BE ESD and Companion Document" respectively. Backup diskettes containing identical information for both the CMC section and the BA/BE section are also provided.

The CMC ESD file is named "BRL0012.003" and the Microsoft Word Companion Document file is named "BRL0012.004". The BA/BE ESD is named "BRL0010.001" and the Microsoft Word Companion Document file is named "BRL0010.002".

Barr Laboratories, Inc. declares that the information provided in the electronic submission is the same as the information provided in the paper submission.

Copies of this letter have been sent to the Baltimore and New York District Offices.

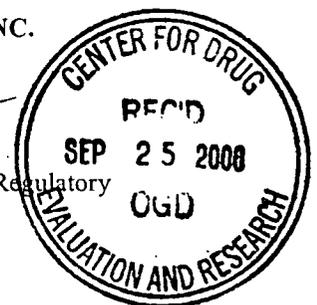
If you have any questions concerning this application, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859. Your earliest acknowledgment to this application will be very much appreciated.

Sincerely,

BARR LABORATORIES, INC.

Pete Baer for

Christine Mundkur
Vice President of Quality and Regulatory
Counsel



Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

March 12, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

~~NEW CORRESP~~
ORIG AMENDMENT
NIFA

REFERENCE: ANDA 75-951
NORETHINDRONE ACETATE TABLETS, USP 5 MG
GENERAL CORRESPONDENCE

Reference is made to our Abbreviated New Drug Application submitted August 25, 2000 under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Norethindrone Acetate Tablets, USP 5 mg. Reference is also made to your facsimile dated February 8, 2001 and Barr's Fax Amendment dated March 9, 2001.

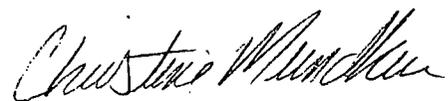
Please note that Barr inadvertently omitted page 08 – 29 containing final printed brochures from the Fax Amendment dated March 9, 2001. Barr is now providing page 08 – 29 containing the final printed brochure. We apologize for any inconvenience this error may have caused.

Field copies of this correspondence have been forwarded to the Baltimore and New York District Offices. A document certification is also provided.

If you have any questions concerning this correspondence, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.



Christine Mundkur
Vice President, Quality and
Regulatory Counsel



Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

March 9, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

ORIG AMENDMENT

NIFA

REFERENCE: ANDA 75-951
NORETHINDRONE ACETATE TABLETS, USP 5 MG
FAX AMENDMENT.

Reference is made to our Abbreviated New Drug Application submitted August 25, 2000 under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Norethindrone Acetate Tablets, USP 5 mg. Reference is also made to your facsimile dated February 8, 2001. The deficiencies identified in the February 8, 2001 facsimile and our responses are as follows:

A. Deficiencies:

Comment 1:

We have the following comments regarding the drug substance:

- Please revise your residual limits to be identical to those of
- Please examine if the drug substance may exhibit Please establish a control based on the material used in the biobatch, if appropriate.

Response:

- Please refer to DMF norethindrone acetate that specifies the limits for residual. Therefore, Barr's specifications for residual are identical to those of
- Available literature indicate that norethindrone acetate may exhibit the following forms:

Primary Form: melting point)
Secondary Form: melting point)

The drug substance manufacturer has confirmed that norethindrone acetate manufactured by them is always the primary form. In the Drug Master File, has also characterized norethindrone acetate as having a melting point of approximately. Based on the information provided by testing of the raw material used in the biobatch and a monograph of norethindrone acetate published in the 1997 Japanese Pharmacopoeial Commission, Barr has established a test for melting point with limits of.

C. Revised test method and specifications with the test for melting point are provided in Attachment 1.



Barr Laboratories, Inc.

Comment 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.

Response:

- a. Barr Laboratories, Inc. believes that the following in-process guidelines and specifications, as summarized below, are appropriate. A brief description of Barr's procedures to establish these in-process parameters and justifications thereof is provided below.

Table 1 – In Process Guidelines and Specifications

Parameter	Target	Guidelines (Average of 10)	Guidelines (Individuals)	Specifications (Average of 10)	Specifications (Individuals)
Weight					
Hardness					
Thickness					

Weight:

The weight guidelines and specifications for Norethindrone Acetate Tablets were established using the procedures employed for all of Barr's products. Barr's in-process guidelines and specifications are based on the specifications established for the finished product. Since assay and content uniformity of the finished product are directly affected by the weight, in-process guidelines and specifications are based on the assay and content uniformity limits. Guidelines are used to control and monitor the process and are set with a tighter range. The weight guidelines for an average of 10 tablets are typically set at % of the target weight, which is very narrow. For this product, the average tablet weight guideline is $\pm 4\%$ of the target weight. The guidelines for individual tablet and the specifications for an average of 10 tablets are based on the assay limit (90.0-110.0%), whereas the specifications for individual tablet weights are based on the content uniformity limits (85.0-115.0%) of the finished product. These specifications are based on established standards for the finished product and provide for occasional variability of a routine process.

Table 2 – Weight Guidelines and Specifications

Parameter	Target	Guidelines (Average of 10)	Guidelines (Individuals)	Specifications (Average of 10)	Specifications (Individuals)

Barr Laboratories, Inc.

✓ **Hardness:**
 Hardness ranges for new products are determined by performing a study on the proposed formulation. Trial batches were manufactured and compressed at hardness levels between [redacted]. Dissolution profiles were generated and compared to each other and to the reference product, to determine the effects of hardness on the release of the drug. The dissolution profiles of tablets compressed at the selected hardness range of [redacted] show that they are comparable (Attachment 2). In addition, the dissolution profiles generated during the hardness studies with the submission batch also support the range specified by Barr (Attachment 2).

✓ **Thickness:**
 Tablet thickness is a function of the tablet weight and hardness. In order to determine the thickness range, tablets from a trial batch were compressed at the guideline limits of the weight and hardness ranges, [redacted] respectively. These limits are defined as (1) maximum weight, minimum hardness [redacted] and (2) minimum weight, maximum hardness [redacted]. In some cases the guideline limits were exceeded, but remained within the specifications, demonstrating worse cases. The following table summarizes the data:

Table 3 – Thickness Studies with Trial Batch

Scale up Batch #: CODC005A	Max. Weight/Min. Hardness (maximum thickness)	Min. Weight/Max. Hardness (minimum thickness)
Size: [redacted] tabs		
Manufactured: 3/3/00		
Weight (mg)		
Hardness (kp)		
Thickness (in)		

As a result of this study, it was concluded that the target thickness of [redacted] inches with a guideline of [redacted] inches is justified. The thickness specifications for individual tablets [redacted] were determined as a percentage of the target thickness and are supported by the data presented above. The data for tablet weight, thickness, and hardness submitted in the original application reflected the normal production run. The data generated during the validation studies performed on the submission batch (see table below) shows the variability of a manufacturing process and supports the thickness specification.

Table 4 – In-Process Data for the Submission Batch

Batch #: 102110001R	Low Hardness Study (Pre Start-up)	High Hardness Study (Pre Start-up)	Target Hardness (Production Run)
Size: [redacted] tabs			
Manufactured: 3/24/00			
Weight (mg)			
Hardness (kp)			
Thickness (in)			

Therefore, as demonstrated by the data from development work and confirmed during the validation studies performed on the submission batch, the current in process guidelines and specifications are justified and are appropriate for this product.

Barr Laboratories, Inc.

- b. Barr has revised its in-process testing for _____ for Norethindrone Acetate Tablets, USP 5 mg as follows:

Test	Limits
Uniformity:	• 3 samples: Between 90.0-110.0%*
	• RSD NMT %
	• 10-12 samples between %*
	• Mean: 90.0-110.0%*
	• RSD NMT %

* of labeled blend potency

Barr's updated In-Process and Finished Product Test Method _____ and corresponding quality control analytical specification test records are provided in Attachment 3.

Comment 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.

Response:

In view of the Agency comment, Barr reviewed the method validation studies and the stability data for potential degradation products. Barr has also consulted with _____ the drug substance manufacturer. According to _____ technical package, none of the impurities identified in the DMF has increased over time. The technical package also states that with the exception of _____ derivative, all other impurities are process related. A summary of _____ stability data is provided in Attachment 4.

Stress studies conducted by Barr indicate that in addition to _____ derivative, norethindrone may also be a potential degradation product. The revised method validation report containing the stress studies is provided in Attachment 5. The stability data generated with the finished product indicate the presence of norethindrone impurity. Data available to date indicate that with the exception of _____ derivative and norethindrone, all other impurities associated with the drug substance are not degradation products. Therefore, Barr has revised the test method, the specifications and the stability protocol to include noethindrone as an impurity for release and stability.

Furthermore, Barr tested the innovator product and observed norethindrone at a level of _____ %. Based on the stability data of Barr's Norethindrone Acetate Tablets, tests performed on the innovator's product and the fact that norethindrone is a major metabolite of noethindrone acetate, Barr has set a limit of _____ % for this impurity. Barr has also validated the method of quantitation for norethindrone impurity. The method validation report RD 01-062 is provided in Attachment 6.

Barr Laboratories, Inc.

Comment 4:

Please clarify your use of bulk packaging. Is it for in-house use or sale to repackagers?

Response:

Barr uses bulk packaging for in-process use only. Barr has no intention of selling bulk finished product. The finished product is temporarily stored in bulk containers after tableting and before being packaged in bottles. Please note that stability testing is performed on bulk to establish in-process hold time. This ensures that the finished product maintains its identity, strength, quality and purity during the time it is stored in bulk containers.

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

Comment 1:

Please submit additional long term stability data for the exhibit batch, if available.

Response:

Long term stability data collected through 9 month for Norethindrone Acetate Tablets, USP 5 mg is provided in Attachment 7.

Comment 2:

Please acknowledge that the USP monograph methods are the regulatory methods and shall rule in the event of a dispute.

Response:

Barr acknowledges that the USP monograph methods are the regulatory methods and shall rule in the event of a dispute.

Comment 3:

Labeling deficiencies will also need to be addressed in your reply.

Response:

Acknowledged.

Comment 4:

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

Response:

Acknowledged.

Barr Laboratories, Inc.

Labeling Deficiencies:

Comment 1:

CONTAINER (50's) – Satisfactory in draft.

Response:

The final printed labels and a side by side comparison is provided in Attachment 8.

Comment 2:

PHYSICIAN'S INSERT

a. **DESCRIPTION –** Revise () to read “anhydrous lactose” in the last sentence of this section.

b. **PRECAUTIONS (General) –**

i. Replace the current number 6 and number seven with the following:

6. Data suggest that progestin therapy may have adverse effects on lipid and carbohydrate metabolism. The choice of progestin, its dose, and its regimen may be important in minimizing these adverse effects, but these issues will require further study before they are clarified. Women with hyperlipidemias and/or diabetes should be monitored closely during progestin therapy.

ii. Renumber the current number 8 and number 9 as number 7 and 8 respectively.

Response:

Barr has revised the package brochure to incorporate the above mentioned changes. The final printed brochure and a side by side comparison is provided in Attachment 8.

Comment 3:

PATIENT PACKAGE INSERT – Satisfactory in draft.

Response:

The final printed patient package insert and a side by side comparison is provided in Attachment 8. Please note that the package brochure and the patient package insert is a combined piece.

Barr Laboratories, Inc.

Bioequivalency Comments

Comment 1:

The Division of Bioequivalence has completed its review and has no further questions at this time.

Response:

Acknowledged.

Comment 2:

We acknowledge that the dissolution testing will need to be incorporated into your stability and quality control programs. Dissolution testing should meet the USP 24 specifications.

Response:

The dissolution testing in accordance with USP 24 has been incorporated into Barr's stability and quality control program.

Comment 3:

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Response:

Acknowledged.

Field copies of this correspondence have been forwarded to the Baltimore and New York District Offices. A document certification is also provided.

If you have any questions concerning this correspondence, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.



Christine Mundkur
Vice President, Quality and
Regulatory Counsel



Barr Laboratories, Inc.

75-951

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

August 25, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

**REFERENCE: ABBREVIATED NEW DRUG APPLICATION
NORETHINDRONE ACETATE TABLETS, USP 5 MG**

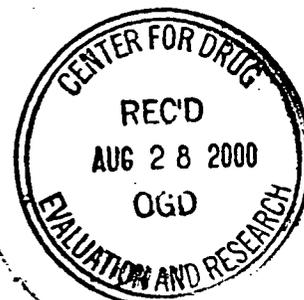
In accordance with the regulations under section 505(j) of the Federal Food and Cosmetic Act, Barr Laboratories, Inc. is submitting an Abbreviated New Drug Application for Norethindrone Acetate Tablets, USP 5 mg.

The application is provided in duplicate, as an archival copy and a review copy. The archival copy of the application is contained in blue binders and consists of 7 volumes. The chemistry, manufacturing and controls part of the review copy is contained in red binders and consists of 2 volumes. The bioequivalence part of the review copy is contained in orange binders consisting of 6 volumes.

Included in this application and in accordance with the Generic Drug Enforcement Act of 1992, are Debarment Certification Statements from Barr and its outside contractors. Field Copies of this application have been forwarded to the Baltimore and New York District Offices. Certifications of financial interests and arrangements of clinical investigators conducting the bioequivalence study are provided in Section VI.

The CMC and BA/BE section of this application will be provided in electronic format within 30 days from this date. Barr Laboratories, Inc. will, at that time, provide a declaration that the information in the electronic submission is the same as the information provided in the paper submission.

The format of this application is in accordance with Office of Generic Drug's Guidance for Industry: Organization of an ANDA, dated February 1999. The information submitted in this application is also in accordance with the October 14, 1994 communication from Dr. Janet Woodcock, (CDER) and Mr. Ronald Chesemore (ORA).



Barr Laboratories, Inc.

If you have any questions concerning this application, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.



Christine Mundkur
Vice President, Quality and
Regulatory Counsel

