CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74517

CORRESPONDENCE

ANDA 74-517

Eon Labs Manufacturing, Inc.
Attention: John Purpura
227-15 North Conduit Avenue
Laurelton, New York 11413

DEC 15 1995

Dear Sir:

This is in reference to your abbreviated new drug application dated June 30, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Guanabenz Acetate Tablets USP, 4 mg and 8 mg (base).

Reference is also made to your amendment dated May 1, 1995.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

1. Regarding inactive ingredients:

   a. COAs for pregelatinized starch and colloidal silicon dioxide should be updated to USP 23/NF 18 to include the organic volatile impurities.

   b. Please update and resubmit your and the manufacturer COAs for iron oxide to conform with USP 23/NF 18. ID, water soluble substances, acid insoluble substances and assay should be included in your COAs to conform with NF 18.(see page 2246 NF).

   c. Since Aluminum interferes with the USP test method please provide for an alternate method to determine heavy metals in FD&C Blue #1 Aluminum Lake and resubmit test results.

2. Regarding manufacturing and processing:

   a. The average weight variation limits for 4 mg and 8 mg tablets are submitted as (%) in your amendment dated May, 1, 1995 (See comment 3 a and 3 b). USP XX is no longer effective. A corrected copy submitted in attachment 6 should reflect your own tighter specifications (%) for average tablet

weights and revised COAs for each strength for the finished product should be resubmitted.

b. As we indicated in our letter dated December 21, 1994, the packaging and labeling reconciliation and limits should be incorporated into your blank production batch records.

3. Regarding container/closures:

a. Please provide the test results for container/closure permeation test <671> USP 23/NF 18 for 100 cc and 150 cc tight containers.

b. In the original ANDA only HDPE bottles have been used as containers. In your amendment dated May 1, 1995, bottles have been added to container/closure systems. Please clarify.

c. Submit <661> test data from all bottle manufacturers prior to the approval of this application.

d. We understand that you are planning to market Guanabenz Acetate Tablets USP, 4 mg in bulk 4 gallon cardboard containers to customers and further request a 6 month expiration date for the product in these containers. Please note that a bulk package of the 4 mg tablets for units in a cardboard container is not an acceptable marketed configuration and cannot be approved as such. Please define the intended use of the bulk package and revise your application accordingly.

4. Regarding laboratory controls:

a. The average weight limit for both strengths was changed to % based on your comment under 3b. Please revise the average tablet weight variations from % in your finished product COAs under changed/updated information and resubmit.

b. The total impurity limit established as NMT % for chromatographic purity and total related compounds, was deleted in your

comment item 5b. But in your revised "Quality Control Finished Tablet & Report Form" for Guanabenz Acetate Tablets USP, 4 mg and 8 mg, you indicate that the limit (NMT %) is given as the total amount of any observed impurity. Please clarify.

5. Regarding method validation:

   a. Please provide minimum detection limits for the z-isomer and aminoguanidine in both bulk drug substance and finished product.

   b. Please provide chromatograms for the fourth degradant (z-isomer) from suitability solution (in 0.1 N HCl) for bulk and formulated material and submit the % recovered amount of guanabenz and z-isomer.

   c. The z-isomer is eluting before guanabenz under the stability indicating conditions (See attachment 15). The z-isomer peak is very high under the extracting UV solvent and 2N HCl for bulk and formulated material. Please provide the % recovered amount of z-isomers and guanabenz acetate under these conditions.

      In addition provide the % recovered amount of guanabenz acetate under other stability indicating conditions which were submitted in Figures 7-15.

6. Regarding stability:

   a. You proposed a total NMT % for total related compounds in stability protocol. This limit is not consistent with the limit you provided for finished products which is any observed impurities is NMT %. Please clarify.

   b. If you would like to use alternate container/closure systems for 4 mg and 8 mg tablets, please provide three months accelerated stability data on bottles with and metal screw caps for 100's and 1000's container/closure systems.

B. Labeling Deficiencies

Insert:

1. DESCRIPTION

   a. Please list your inactive ingredients in alphabetical order.

   b. Specify the type of iron oxide used in your inactive ingredients.

2. CONTRAINDICATIONS

   Revise the title heading to read "CONTRAINDICATIONS", [plural].

3. PRECAUTIONS

   a. Use the term "guanabenz" rather than "guanabenz acetate" in the last sentences of the fourth and fifth paragraphs.

   b. Pediatric Use

      ... in pediatric patients less than ...

4. ADVERSE REACTIONS

   Use the term "guanabenz" rather than "guanabenz acetate" in the first and last sentences of the fourth paragraph.

5. HOW SUPPLIED

   Please describe the 4 mg tablet as an "unscored" tablet.

Please revise your insert labeling and then prepare and submit final printed insert labeling.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

The USP 23/NF 18 was effective January 1, 1995. The specifications and test methods for drug substance and drug product should be updated to comply with USP 23/NF 18.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 12/15/95

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-517

Eon Labs Manufacturing, Inc.
Attention: Edward Shinal, Ph.D.
227-15 N. Conduit Avenue
Laurelton, NY 11413

SEP 1 1994

Dear Sir:

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

NAME OF DRUG: Guanabenz Acetate Tablets USP, 4 mg and 8 mg

DATE OF APPLICATION: June 30, 1994

DATE OF RECEIPT: July 1, 1994

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:

Timothy Ames
Consumer Safety Officer
(301) 594-0305

Sincerely yours,

/S/

Robert W. Pollock 9-1-94
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-517
cc: DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-615/MBennett

AIP status entered.

Endorsement: HFD-615/GJohnston, Chief_____date
HFD-615PRickman, CSO_____date 8/31/94
HFD-615/WRussell, CSO /S/ date 8/22/94
HFD-647, Supervisory Chemist_____date
WP File\russell\74-517
F/T bcw/8-22-94
ANDA Acknowledgement Letter!

Guanabenz Acetate Tablets USP, 4 and 8 mg
ANDA 74-517

NOV 14 1995

Eon Laboratories, Inc.
Attention: Edward Shinal
227-15 Conduit Ave.,
Laurelton, NY 11413

Dear Dr. Shinal:

Reference is made to the bioequivalence data submitted on June 9, 1995, for Guanabenz Acetate Tablets USP, 4 mg and 8 mg.

The Office of Generic Drugs (OGD) has reviewed the submitted data and the following items were found to be deficient:

1. The response stated that the addition of internal standard (IS) into plasma should not be considered as a change in assay SOP since this was the procedure used in assay development.

   This is unclear since the analytical notes state. "Analyses were halted and the IS addition technique was evaluated. As a result, analysts were instructed to add internal standard solution directly into the plasma layer and avoid contact with the test tube wall." If the addition of IS directly to the matrix was used in assay development then the statement related to stopping and re-instructing the analysts is confusing. If direct addition of IS to the matrix was the procedure used during assay development why was that procedure not followed during the processing of samples? Otherwise it appears that there were in fact two existing SOP's, one which added IS to the matrix and one which did not. Your explanation does not clarify the situation. Please supply validation information, including chromatograms, obtained using both methods of IS addition. This information should also explain when each assay was developed since the clinical study was conducted from 7/21/93 to 7/29/93 and the samples were frozen until analyzed on 4/94. The pre-study validation was done on 3/25/94 with a mid study validation done on 4/21/94(samples were analyzed from 4/94 to 5/94).

2. Please explain why the importance of adding IS directly into the matrix was not fully appreciated by the production staff. In addition, please provide an explanation as to why the performance of a properly validated assay was adversely affected by the pace of sample processing. Any relevant data to support and clarify this finding should be submitted.

3. A detailed SOP for sample analysis was requested in comment #1 of our April 24, 1995 correspondence. This was not submitted and is required for review. Additionally, the processing procedures in the submission were marked as confidential and contained no information. Please submit the complete processing procedures for review.

4. Explain how a properly validated assay can exhibit different performance characteristics depending upon the analyst? All pertinent data that would help clarify this phenomenon should be submitted.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-517

Eon Labs Manufacturing, Inc.
Attention: Edward Shinal, Ph.D.
227-15 North Conduit Avenue
Laurelton, New York 11413

DEC 21 1994

Dear Dr. Shinal:

This is in reference to your abbreviated new drug application dated June 30, 1994, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Guanabenz Acetate Tablets USP, 4 mg and 8 mg.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

1. Regarding components and composition:

   a. Please revise your component and composition statement to indicate the type of microcrystalline cellulose (Avicel).

   b. Please revise your component and composition statement to include the type of iron oxide.

2. Regarding inactive ingredients:

   a. Please update and resubmit manufacturer COA for anhydrous lactose to include the loss on drying, protein and light absorbing impurities to conform with NF XVII.

   b. Please provide specifications for synthetic iron oxide according to 21 CFR 73.1200(b) and the amount of elemental iron based on a maximum daily dose of Guanabenz Acetate tablets, in order to comply with 21 CFR 73.1200 (c) which limits the amount of elemental iron to NMT mg per day.

   c. Please update and resubmit your and manufacturer COAs for iron oxide to conform with NF XVII, Supplement 6.

   d. The color additive FD&C Blue #1 shall conform with the requirements of 21 CFR 74 1101. Please provide test methods, specifications and assay test results for FD&C Blue #1

Aluminum Lake for total color, heavy metals and water insoluble matter.

3. Regarding manufacturing and processing:

   a. The average weight limits for 4 mg %) and 8 mg %) tablets are very wide. Please resubmit tightened specifications.

   b. Please submit individual weight variation limits for 4 mg and 8 mg tablets.

   c. Please submit thickness limits for both strength tablets.

   d. Submit assay test results for active ingredients from top, middle and bottom of blender during in-process blend uniformity testing. Blend uniformity test limits should be included in your master batch records.

   e. The innovator's 8 mg product is scored whereas your 8 mg product is not scored. Please note the following:

      i. The 8 mg tablet must be scored.

      ii. We request that you commit to provide the following information for the first production batch manufactured. This data must be submitted and found satisfactory prior to release of the batch for marketing.

         a. The executed batch record reflecting the manufacture of an scored tablet and a complete certificate of analysis for the batch.

         b. A comparative dissolution profile of the unscored vs scored tablets.

      Please submit this information, when available, as a new correspondence to the ANDA. Please also alert the consumer safety officer (Timothy Ames, telephone number (301-594-0309) so that this information can be promptly reviewed. The Agency's decision on the acceptability of the data will be communicated to you.

   f. The packaging and labeling reconciliation limits should be submitted and incorporated

in your blank production batch records.

g. Under item 7 of our letter to the regulated industry dated November 8, 1991, it was clearly stated that the bioequivalence or test batch should be packaged entirely if manufactured after January 1, 1992. Please provide justification for the partial packaging and a protocol to support the partial packaging of the test batches.

4. Regarding container/closures:

a. Please provide the test results for container/closure permeation test <671> USP XXII/NF XVII for tight containers.

b. Please provide your COAs for containers per <661> and container/closure permeation test <671> USP XXII/NF XVII.

c. Please provide COA for purified cotton per USP XXII.

d. Please submit DMF authorization letter for

e. Please submit both application and removal torque results for tight containers as per USP XXII/NF XVII.

f. Please submit complete container/closure system information for 4 mg tablets bottles of 100.

g. The 4 gallon cardboard container has been used as a bulk container for the 4 mg tablets. Please refer item # 3.g. regarding partial packaging and respond.

5. Regarding laboratory controls:

a. Please revise the average tablet weight variations in your finished product COAs and resubmit.

b. Your specifications for Chromatographic purity %) and total related compounds %) together are too high (total %). Total related compounds should be included into chromatographic purity limits as NMT % for individual and NMT % for total impurities. Please revise your specifications and resubmit.

c. Please revise your finished product specifications and COAs for total related compounds and resubmit.

6. Regarding method validation:

a. Please provide minimum detection limits of the degradation products in both bulk drug substance and finished product.

b. Please submit the HPLC chromatograms of degradation products and impurities for the bulk drug substance and finished dosage forms showing the identities of the peaks and retention times.

7. Regarding stability:

a. The limit of NMT % for total related compounds and chromatographic purity is too high (total %). Total related compounds should be included into chromatographic purity limits as NMT % for individual and NMT % for total impurities. Please revise your specifications and resubmit.

b. Please revise your stability protocol and data reporting forms to include the new limits for total related compounds and resubmit.

c. Your stability reports indicate that metal cap was used as a closure for 4 mg tablets, 100 count. The innovator uses child resistant closures on the smallest configurations of both strengths. You should be using a child resistant closure on the bottles of 100 for the 4 mg dose. Please address.

B. Labeling Deficiencies

COMMENTS:

Container: **4 mg and 8 mg, 100's and 1000's**

1. We encourage you to differentiate between your different product strengths by using boxing and/or contrasting colors.

2. Increase the prominence of the product strength.

3. Include the statement, "Protect from light" to follow the "Protect from moisture" statement.

Insert:

1. **DESCRIPTION**

   a. Include the molecular formula.

      $C_8H_8Cl_2N_4 \cdot C_2H_4O_2$

   b. Please note, lactose is now the subject of two official monographs listed in the USP. We refer you to USP XXII/NF XVII-Supplement 9 for further guidance. Please revise to reflect the anhydrous material.

   c. Please revise the description of this drug product to be consistent with the Description and Solubility information listed in the USP.

2. **INDICATIONS AND USAGE**

   Sentence 1 -

      Guanabenz acetate tablets are indicated ...

3. **PRECAUTIONS**

   a. Carcinogenesis, Mutagenesis, Impairment of Fertility,
   paragraph 1 (sentence 1) -

      ... at doses up to 9.5 mg/kg/day, ...

      [When expressing a dose, please assure that the "mg/kg/day" appears on the same line as the corresponding numerical value].

   b. Pregnancy

      i. Revise as follows:

         PREGNANCY
         Teratogenic Effects:Pregnancy Category C
         GUANABENZ ACETATE MAY HAVE ADVERSE...
         [NOTE: Delete the underline in the subsection heading and add "Teratogenic Effects":

ii. Sentence 1 -

... human dose of 1 mg/kg.
[delete the terminal zero]

4. **DOSAGE AND ADMINISTRATION**

Paragraph 1 -

Dosage with guanabenz acetate tablets should ...

5. **HOW SUPPLIED**

a. Indicate whether tablets are scored or unscored (See item 3e chemistry deficiencies).

b. We encourage the inclusion of the NDC numbers in the HOW SUPPLIED section.

c. Add the statement, "Keep tightly closed".

6. **GENERAL COMMENT:**

Please refer to the enclosed Wytensin labeling, for guidance in determining when to use guanabenz, guanabenz acetate or guanabenz acetate tablets.

Please revise your container labels and insert labeling, then prepare and submit final printed container labels and draft insert labeling.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. You will be notified in a separate letter of any deficiencies in the bioequivalence portion

of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/

Florence S. Fang
Acting Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: Enclosure

Guanabenz Acetate Tablets USP, 4 mg and 8 mg
ANDA 74-517

APR 24 1995

Eon Laboratories, Inc.
Attention: Edward Shinal
227-15 Conduit Ave.,
Laurelton, NY 11413

Dear Dr. Shinal:

Reference is made to the *in vivo* bioequivalence study, waiver of *in vivo* bioequivalence and supporting dissolution data submitted on June 30, 1994, for Guanabenz Acetate Tablets USP, 4 mg and 8 mg.

The Office of Generic Drugs has reviewed the submitted material and have determined that the bioequivalence data is incomplete for the following reasons:

1. On page 3 of analytical notes the study report states "the chromatograms from the initial analysis of subjects #2, 6, 7, 8, 9, 14 and 15 did not meet acceptance criteria .... Analysis was halted and the internal standard addition technique was evaluated. As a result, analysts were instructed to add internal standard solution directly into the plasma layer and avoid contact with the test tube wall." The procedure of allowing a change in SOP during the actual analysis of samples is highly unusual. Supply the original SOP for analysis. Based upon the fact that the method was changed during analysis, a complete assay validation should be done for the altered assay. Also, why were the samples for the subjects in question not listed as repeats?

2. The procedure used to replot chromatograms had a very low response for guanabenz. For example, the 0.15 st #31 on the original chromatogram at a retention time of 3.90 min had no peak. However, when it was replotted the same sample had a retention time of 3.87 min and a height of 2719. On the other hand the internal standard retention time remained at 6.80 min with a peak height of 299561. This is a very unusual result. Please submit details of the replot procedure for review.

3. On several of the samples, including replots, the chromatographic peak seemed to be somewhat compromised by noise or an interference on the shoulder. Close scrutiny of the retention times for several of these chromatograms indicated different retention times from the computer sheet.

   For example:

sample #	sample name	computer rt	chromatogram rt
27	0.3stda	3.88	3.89
30	83088	3.88	3.89

4. Please supply all chromatograms for the 0.15 ng/ml standards and plasma blanks to the Division of Bioequivalence for evaluation based upon the problematic chromatography exhibited by the 0.15 ng/ml standards.

5. The waiver of requirements for *in vivo* bioequivalence can not be considered until the *in vivo* bioequivalence study on the 8 mg product has been deemed acceptable. The waiver request should be resubmitted along with the amendment to the *in vivo* study.

An action described under 21 CFR 314.96 which will amend this application is required, if you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290.

In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research