CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74517

BIOEQUIVALENCY REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:74517 APPLICANT:Eon Labs

DRUG PRODUCT:Guanabenz Acetate 4 mg and 8 mg Tablets

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

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.

Sincerely yours,

/S/

Dale Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

File ANDA 74-517

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74517 SPONSOR :Eon Laboratories
DRUG & DOSAGE FORM :Guanabenz Acetate Tablet
STRENGTH (s) : 4 mg and 8 mg
TYPE OF STUDY:SD
STUDY SITE: CLINICAL :
ANALYTICAL : Same as Clinical

STUDY SUMMARY : See Review

Parameter	test	ref	ratio	90% CI (log).
Cmax(ng/ml)				
AUC(0-T) ngxhr/ml				
AUC(0-Inf)ngxhr/ml				
Tmax hr				
Half-life hr				

DISSOLUTION :See Review
Conditions: USP paddle
1000 ml Water ,50 RPM

Time(min)	Test Mean(range)	Ref. Mean(range)
Q = NLT % in 60 min		

PRIMARY REVIEWER : Andre Jackson BRANCH : I

INITIAL : AJ DATE : 4-16-98

BRANCH CHIEF :Y.C. Huang BRANCH :I

INITIAL : YCH DATE : 4/16/98

DIRECTOR
DIVISION OF BIOEQUIVALENCE: D.P. Conner

INITIAL : DPC DATE : 4/16/98

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL : _____ DATE : _____

Guanabenz Acetate
4 mg Tablet
8 mg Tablet
ANDA # 74-517
Reviewer: Andre Jackson
WP # 74-517C.097

Eon Labs
Laurelton, N.Y.
Submission Dated:
October 1, 1997
February 18, 98
March 19, 98
March 23, 98
diskette

REVIEW OF STUDY CORRESPONDENCE

Background:

The firm submitted a single dose fasting on June 30, 1994 which was found to be incomplete. This submission is the firm's second response to the deficiencies from the original study.

Deficiency 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).

Firm's Response: Prior to subject sample analysis for any given assay the analysts and R&D chemistry meet to discuss the assay

and review the procedure. During the review of this method with the analysts the chemist verbally emphasized that IS should be added directly to the matrix and not just to the tube. However, this was not included in the written procedure. We admit that this omission of information was an error. For the guanabenz procedure there should have been written clarification regarding IS addition directly to the plasma surface since the chemist confirms that this was the method of IS addition used in validation. This method of IS addition was not typical for most of the assays performed at the time and may partially explain but definitely not excuse,the way in which some analysts performed IS addition.

Once subject sample analysis began, it was noticed that two of the three analysts had run failures due to excessive IS variability, however the third analyst, who also participated in the validation of the method, had no run failures due to IS variability. At that point analysis was stopped and it was re-emphasized that IS must be added directly to the plasma surface. When subject sample analysis was re-started the runs as well as the IS peak heights were substantially more consistent than before.

Enclosed with this response are validation data related to the variability we observed in IS peak height. Chromatograms 1 and 2 correspond to the 0.3 and 6.0 standards denoted in Table 1(*) while chromatograms 3 and 4 correspond to the same concentration and standards denoted in Table 3. Tables 1 and 2 contain standard curve linearity and precision data with a chemist adding IS via a repeater pipette (not uniformly into the plasma matrix), while Tables 3 and 4 contain standard curve linearity and precision data with the IS added via a single action pipetting device directly onto the plasma surface. The tabulated data shows that the IS (2-NBA) response was more variable (as %RSD) and had more values outside of the acceptable range (±25%) of the mean IS peak height) when IS was not routinely added to the plasma surface. The %RSD in Table 1 and 2 were 16.40 and 12.42 while those in Tables 3 and 4 were 7.72 and 6.62 respectively. In addition IS peak height failures occurred with the runs shown in Tables 1 and 2 but did not occur in the runs depicted in Tables 3 and 4. The chromatograms submitted are typical of those observed with this assay (also as per final report) with the retention time of guanabenz and the IS (2-NBA) depicted. As can be seen in

chromatograms 1 and 2 the IS peak height was outside the acceptable range however, for chromatograms 3 and 4 no abnormalities in IS peak height are present.

Prior to the development and validation of the current assay we had a previously validated guanabenz assay that utilized a different processing procedure than that used in this assay. At the time the study was conducted a new Director of Research and Development, Dr. Dwight D. Stiff was hired. Dr. Stiff evaluated the method and found it to be exceedingly long and cumbersome (24 processing steps). Since we had documented sample stability for 296 days we chose to re-develop the assay to make it simpler to perform and improve upon its performance and ruggedness, and at the same time re-validate the assay to meet the current laboratory standards. Although the re-development and validation took longer than expected, study sample analyses were completed , within the established frozen stability time frame of 296 days.

FDA Reply

The firm's response is acceptable.

Deficiency 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.

Firm's Response-

For the reasons given above, all of the analysts did not consistently add IS directly to the plasma surface upon the initiation of subject sample analysis. During validation of the assay, the IS was added directly to the plasma surface with a single action air displacement pipette since addition of IS with a repeating pipette coincided with increased peak height variability. Addition of IS with the repeating pipette cannot be done consistently directly into the matrix in the extraction tube due to its large size.

The statement regarding the pace of sample processing was included in the original response as a possible co-factor in early run failures in that the analysts may have been, although this cannot be determined with certainty, more prone to have aberrant IS peak heights due to improper addition of IS directly into the matrix.

FDA Reply

The firm's response is acceptable.

Deficiency 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.

Firm's Response

We are sorry for the omission of these items from our original response. Enclosed are copies of the analytical SOP's utilized for various phases of subject sample analysis. These documents were those in effect during the time of subject sample analysis for the guanabenz study. Since Novum was formerly known as Biodecision some of these documents contain the Biodecision header since at that time they had not been revised and re-issued with the Novum header. In addition, we have also enclosed the complete processing procedure for the guanabenz assay for your review.

FDA Reply

The firm's response is acceptable.

Deficiency 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 detailed in response to Question 1. The different performance characteristics between analysts was due to two of the analysts not adding the IS to the matrix correctly. As soon as this problem had been reviewed and all analysts were working to a standardized procedure, the between analysts variation was significantly reduced. We believe the between analyst variation on the standardized method was within acceptable limits.

FDA Reply

The firm's response is acceptable.

RESULTS

Tables for mean data are included in this review since they were not included in the original review due to questions related to the validity of the assay.

TABLE 1. Mean guanabenz plasma concentrations ± SD.

	Time	Test	SD	Reference	SD
CONC01	0.00	0.0000	0.0000	0.0000	0.0000
CONC02	0.50	0.3612	0.2868	0.6001	0.3496
CONC03	1.00	1.7275	0.8490	2.1919	1.2087
CONC04	1.50	2.7380	1.1697	2.9924	1.5029
CONC05	2.00	3.0587	1.2937	3.1664	1.3388
CONC06	2.50	3.1019	1.3163	3.1631	1.2327
CONC07	3.00	3.1516	1.3196	3.2469	1.3349
CONC08	3.50	3.1013	1.2935	3.1286	1.2027
CONC09	4.00	3.0652	1.2927	3.1216	1.2466
CONC10	5.00	2.8326	1.3705	2.8349	1.2081
CONC11	6.00	2.5795	1.3625	2.5840	1.3407

CONC12	8.00	1.9946	1.1236	1.9456	0.9210
CONC13	10.0	1.5183	0.8517	1.5312	0.8829
CONC14	12.0	1.0434	0.6078	1.0819	0.5887
CONC15	16.0	0.5319	0.3181	0.5434	0.3054
CONC16	20.0	0.3128	0.2061	0.3235	0.2242
CONC17	24.0	0.1883	0.1682	0.1909	0.1642
CONC18	28.0	0.1033	0.1318	0.0996	0.1309

Table 2. Mean pharmacokinetic parameters ± SD for the subjects in the guanabenz study.

	Test	SD	Reference	SD	Ratio (T/R)
AUC	31.92	15.66	32.85	14.83	0.97
AUCINF	33.97	16.29	34.77	15.30	0.98
CMAX	3.68	1.30	3.84	1.44	0.96
TMAX	3.00	1.17	2.85	1.37	--
KE	0.12	0.03	0.12	0.03	---
ELIM					
Half-Life	6.15	2.06	6.01	1.37	
LNAUC[1]	27.93		28.79		0.97
LNAUCI	29.96		30.88		0.97
LNCMAX	3.42		3.52		0.97

[1] Geometric Mean

Table 3.90 % Confidence Intervals

Parameter	
LNAUCL	89-105
LNAUCI	89-105
LNCMAX	87-107

ALL CALCULATIONS WERE VERIFIED BY THE REVIEWER

Comments:

1.The 90 % confidence intervals for quanabenz are within the

acceptable limits of 80-125% of the reference.

2.The dissolution data was previously found to be acceptable. The method was a USP procedure.

3.The 4 mg tablet was previously shown to be compositionally proportional to the 8 mg tablet.

Recommendation

1. The fasting bioequivalence study conducted by Eon on its 8 mg Guanabenz tablet, lots 930402 comparing it to Wyeth Ayerst's Wytensin^{R} 8 mg tablet has been found to be acceptable by the Division of Bioequivalence. The study demonstrates that Eon's 8 mg Guanabenz tablet, is bioequivalent to the reference product Wytensin^{R} 8 mg tablet manufactured by Wyeth Ayerst.

2. The *in vitro* dissolution testing conducted on the 8 mg strength (lot # 930402) and 4 mg strength(lot # 930802) is acceptable. The firm has conducted an acceptable in vivo bioequivalence study dated June 30 ,1994 comparing its 8 mg tablet of the test product with the 8 mg tablet of Wytensin manufactured by Wyeth Ayerst. The formulation for the 4 mg strength is proportionally similar to the 8 mg strength of the test product which underwent bioequivalency testing. The waiver of in vivo bioequivalence study requirements for the 4 mg tablet of the test product is granted. The 4 mg tablet of the test product is therefore deemed bioequivalent to the 4 mg tablet of Wytensin manufactured by Wyeth Ayerst.

3. The in vitro dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 1000 mL of water at 37 C using USP apparatus II paddle at 50 rpm. The test product should meet the following specifications:

NLT % of the labeled amount of the drug in the dosage form is dissolved in 60 min.

Andre J. Jackson /S/
Division of Bioequivalence
Review Branch I

RD INITIALLED YC HUANG
FT INITIALLED YC HUANG /S/ Date: 4/9/98

Concur: /S/ Date: 4/15/98
Dale P. Conner, Pharm.D.
Director,
Division of Bioequivalence

cc: ANDA 74-517 (original, duplicate), HFD-650(Director), HFD-652 (Huang, Jackson), Drug File, Division File.

OCT 25 1995

Guanabenz Acetate
4 mg Tablet
8 mg Tablet
ANDA # 74-517
Reviewer: Andre Jackson
WP #74517C.695

Eon Labs
Laurelton, N.Y.
Submission Dated:
June 9, 1995

Review of Correspondence Related to a Fasting Bioequivalence Study

Background

The firm submitted a bioequivalence study for their 8.0 mg tablet along with a waiver request for the 4.0 mg tablet strength on June 30, 1994. The study was found to be incomplete due to irregularities related to the conduct of the assay. Several questions related to the SOP used by the firm were raised by the Division of Bioequivalence. The current submission is the firm's reply to those deficiencies.

Deficiency 1:

On page 3 of analytical notes the firm states" the chromatograms from the initial analysis of subjects #2, 6, 7, 8, 9, 14 and 15 did not meet acceptance criteria..... Analyses were 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. The firm should supply the original SOP for their analysis. Based upon the fact that the method was changed during analysis the firm should do a complete assay validation for the altered assay. Also why weren't the samples for the subjects in question listed as repeats?

Firm's Reply:

The firm stated that the change in the method of addition of the internal standard (IS) during the course of analysis of subject samples should not be considered as a change in assay SOP since this was the procedure used in the development and validation of the assay. The chemists, at the time, noticed that IS peak

heights were much more variable when the IS was not delivered into the matrix. Validation of the method through the addition of the internal standard solution directly into the matrix improved peak height consistency.

The importance of adding the IS directly into the matrix **was not fully appreciated by all members of the production staff involved in the analysis of the study samples.** Consequently, IS was being added to the tubes containing sample, standard or control but not necessarily, or consistently, directly into the actual matrix. This in turn led to the variable peak heights observed. **Moreover, the pace of sample processing increased during the production analysis of study samples as compared to the pre-study analyses.** We believe this made a substantial contribution to the increased incidence of IS peak height fluctuation.

Subject sample analyses 1-15 were processed and analyzed over a period of 7 days. This pattern of analysis, combined with high sample through-put, time consuming data and chromatographic analysis, and run failure due to variable circumstances precluded the early detection of the IS variability. The procedure was reviewed..... **Also, additional instruction was given to the analysts at that time, regarding steps of the procedure(transfer steps) so as to insure that all of the analysts processed the samples in an identical manner.**

Prior to this meeting, three analysts had been involved in sample processing. One of these analysts, YA, also participated in the validation of the assay. Of the runs that failed due to IS peak height variability, analyst KG processed subjects 2,6,7,14, and 15 while analyst KG processed subjects 8 and 9. Analyst YA, who had validation experience with the method, had no run failures due to variable IS peak heights.

After analyst..... were re-analyzed. During.....failed. As such, analyses performed after additional analyst training were more consistent than those done prior to the retraining session.

Deficiency 2:

The firm used a procedure to replot chromatograms that 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. The firm should supply the details of their replot procedure to

the Division of Bioequivalence for evaluation.

Firm's Reply-

The firm supplied information on their integration and tangent skimming procedure which allows them to quantitate guanabenz in the case when the peak of interest was a shoulder on an interfering peak. They showed how this was applied to the chromatogram #31 that was discussed in the deficiency.

Deficiency 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

Firm's Reply-

The firm explained that these differences between the printed retention times and those in the summary table were due to the data system, Turbochrome used in the study. Retention times are calculated to 1/100 of a minute. For example, 3.886000 would appear as 3.89. However, when the data was printed in the summary table, the data are truncated and not rounded. Therefore, 3.886000 is truncated as 3.88 even though the chromatogram has been rounded to 3.89.

Deficiencies:

1. The firm stated that the addition of 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 firm stated." Analyses were halted and the internal standard addition technique was evaluated. As a result, analyst 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 analyst is confusing. Since direct addition of IS to the matrix was the procedure used during assay development why was it 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. The firm's explanation did not clarify the situation. The firm should 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. The firm should explain why the importance of adding IS directly into the matrix was not fully appreciated by the production staff. Secondly, the firm should explain why the performance of a properly validated assay was adversely affected by the pace of sample processing. Any relevant data the firm has to support and clarify this finding should be submitted to the Division of Bioequivalence.

3. The firm did not submit a detailed SOP for sample analysis as was requested in deficiency 1 related to the June 30, 1995, submission. Processing procedures in the submission were marked confidential and contained no information.

4. The firm should explain how their properly validated assay exhibited different performance characteristics depending upon the analyst? All pertinent data that would help clarify this phenomenon should be submitted to the Division of Bioequivalence.

Recommendation:

1. The bioequivalence study conducted by Eon Labs on its 8.0 mg guanabenz tablet, lot 930402, comparing it to Wyeth Ayerst's Wytensin 8.0 mg tablet has been found to be incomplete by the Division of Bioequivalence. The firm should receive deficiency comments 1-4.

Andre J. Jackson /S/ 10/25/95
Division of Bioequivalence
Review Branch I

RD INITIALLED YCHUANG
FT INITIALLED YCHUANG /S/ 10/25/95

cc: ANDA 74-517 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (Cviswanathan), HFD 652 (Huang, Jackson), Drug File, Drug Division

AJJ/102495/dbm/WP #74517C.695
1st Draft 10/24/95

1.1

OCT 25 1995

Guanabenz
4 mg Tablet
8 mg Tablet
ANDA # 74-517
Reviewer: Andre Jackson
WP #74517SDW.694

Eon Labs
Laurelton, N.Y.
Submission Date:
June 30, 1994

Addendum to Review

The original review listed the assay method as This statement was incorrect.
The assay was done using

/S/ 10/25/95

Andre J. Jackson
Division of Bioequivalence
Review Branch I

RD INITIALLED YCHUANG
FT INITIALLED YCHUANG /S/ 10/25/95

cc: ANDA 74-517 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (Cviswanathan), HFD-652 (Huang, Jackson), Drug File, Drug Division

AJJ/102595/dbm/WP #74517SDWA.694
1st Draft

APR 10 1995

Guanabenz
4 mg Tablet
8 mg Tablet
ANDA # 74-517
Reviewer: Andre Jackson
WP #74517SDW.694

Eon Labs
Pomona, N.Y.
Submission Dated:
June 30, 1994

Review of Fasting
Bioequivalence Study and Dissolution Data and Request for Waiver

Background

Guanabenz acetate is a centrally active hypotensive agent. It appears to stimulate alpha2-adrenergic receptors in the CNS and cause inhibition of sympathetic outflow from the brain.

Guanabenz is indicated in the treatment of hypertension and may be employed alone or in combination with a thiazide diuretic. The side effects of guanabenz are generally mild, and include dry mouth, drowsiness/sedation, dizziness, weakness, and headache.

Following an oral dose about 75% of the drug is absorbed. Because of extensive first-pass metabolism, the bioavailability is low. Following a 16 mg dose, peak levels are about 2.4-2.7 ng/ml at 2-5 hours. The elimination half-life of guanabenz averages 4-9 hours in healthy men. Guanabenz metabolites are excreted mainly in urine (70-80%).

Objective:

The aim of this study is to compare the oral absorption of guanabenz tablets manufactured by Eon Labs with a commercial lot of the reference product, Wytensin^{R} tablets manufactured by Wyeth Ayerst following a dose of two 8 mg tablets.

Methods:

The study was conducted by

Samples were analyzed by

I. Characterization of Study Group:

A. Inclusion criteria
   1. All volunteers selected for this study were male volunteers between the ages of 18 and 45 years. Weight

II. Study Conduct

The study was done in 28, healthy males.

A. Subjects fasted 10 hours overnight until 4.0 hrs after their scheduled dosing times. Water was not allowed from 2 hours before until 2 hours after dosing but was allowed ad lib thereafter.

Standard meals were provided at 4 and approximately 10 hours after dosing.

B. The products employed in the study were:

1. Test: Eon Labs 8.0 mg guanabenz tablet, Lot # 930402, Lot Size tablets, potency %.

2. Reference product: Wyeth Ayerst 8.0 mg Wytensin tablet, Lot#9920413, potency %, expiry date 5/95.

There was a 7 day washout between doses.

C. A 16.0 mg dose (2 x 8.0 mg) of each product (test and reference) was administered at time zero with 240 ml of water. The randomization scheme is presented in table 1.

Table 1. Random Assignment of 28 subjects

Sequence	SUBJECT
A,B	2,4,7,8,9,11,13,17,18,19,21,22,24,27
B,A	1,3,5,10,12,14,15,16,20,23,25,26

Treatment A: guanabenz tablets, 8.0 mg (2 tablets) Eon

Treatment B: Wytensin tablet, 8.0 mg (2 tablets) Wyeth Ayerst

The formulation for the 8.0 mg tablet is given in table 2.

Table 2. COMPOSITION OF THE 8.0 MG Guanabenz Tablet

INGREDIENTS	Amount/Tab
Guanabenz Acetate, USP	mg
Anhydrous Lactose, NF	mg
Microcrystalline Cellulose	mg
Pregelatinized Starch	mg
Sodium Starch Glycolate	)mg
FD&C Blue No.1 Aluminum Lake	mg
Colloidal Silicon Dioxide,NF	mg
Magnesium Stearate,NF	mg
Iron Oxide, Dark Brown #33300	mg

D. Plasma was collected pre-dose and at the following times post-dose: 0.50, 1.0, 1.5, 2, 2.5, 3,3.5, 4,5,6,8,10, 12, 16,20,24,and 28 hours.

E. During the study subjects were monitored for adverse reactions. Blood pressure and pulse rates were measured pre-dose, then at 0.5,1,1.5,2,3,4,6,8,10,12 and 24 hours.

III. Analytical

Assay sensitivity:

The assay was linear over the range of ng/ml. The limit of sensitivity of the assay was defined as 0.15 ng/ml, with values less than this reported as zero.

Precision and Reproducibility:

Reproducibility was assessed by comparing the results of standard samples assayed on different days. The coefficient

of variation was % at a concentration of ng/ml and % at ng/ml.

Inter-day accuracy was assessed by comparing the results of quality control samples analyzed on different days. The coefficient of variation was 8.8% at a concentration of ng/ml and % at ng/ml.

Absolute recovery of guanabenz was :

Conc.	Recovery
ng/ml	50.1%
ng/ml	46.6%

Long Term Stability

The long term stability study was done by comparing replicates of stored samples(296 days) at the concentrations of ng/ml. The stability samples were quantified by preparing fresh duplicate standard curves.

Time Days	Mean	SD	N	Mean	SD	N
0	1.65	0.105	12	6.45	0.306	12
63	1.88	0.283	12	6.41	0.555	12
90	1.49	0.207	12	5.81	0.600	12
296	1.65	0.144	12	6.23	0.388	12

Freeze Thaw

The freeze thaw stability study was done by comparing replicates of stored samples which had been frozen and thawed 5 times at the concentrations of ng/ml.

Time Days	Mean	SD	N	Mean	SD	N
0	0.379	0.045	5	11.6	0.795	5
1	0.354	0.035	5	10.8	0.269	5
2	0.376	0.032	5	12.0	0.558	5
3	0.376	0.025	5	11.3	0.922	5
4	0.352	0.025	5	10.9	0.849	5
5	0.375	0.032	5	10.9	0.845	5

IV. Pharmacokinetic Methodology

Area under the curve(0-t) and AUC(0-inf) was calculated as well as elimination parameters for each subject and dosing group. Observed values for Tmax and Cmax were also reported.

V. Statistical Evaluation

ANOVA was performed at an alpha=0.05 using the GLM procedure of SAS. The model contained the effects of subject within sequence, sequence, period and treatment. Sequence effects were tested against the mean square term for subjects within sequence. All other main effects were tested against the mean square error term. The power to detect a 20% difference between formulations and the 90% confidence intervals for this difference was calculated for each ANOVA.

Log-transformed data was submitted for analysis.

Results

Results will not be presented due to several questions related to analytical methodology.

Adverse Effects

Adverse effects appeared to be equally distributed for the test and reference product and are summarized in table 3.

Subject Drop outs

The study began with 28 volunteers. There were no drop-outs.

Sample reassays:

Only 38 samples were reassayed out of 476 analyzed. (1.2%)

Comments

1. The dissolution data presented by the firm is acceptable.

2. The comparative formulation data for the 4 mg and 8 mg tablets are presented in table 4.

Deficiencies:

1. On page 3 of analytical notes the firm states" the chromatograms from the initial analysis of subjects #2, 6, 7, 8,

9, 14 and 15 did not meet acceptance criteria..... .
Analyses were halted and the internal standard addition technique was evaluated. As a result, analyst 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. The firm should supply the original SOP for their analysis. Based upon the fact that the method was changed during analysis the firm should do a complete assay validation for the altered assay. Also why weren't the samples for the subjects in question listed as repeats?

2.The firm used a procedure to replot chromatograms that 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. The firm should supply the details of their replot procedure to the Division of Bioequivalence for evaluation.

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.The firm should supply all chromatograms for their 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.

Recommendation:

1. The bioequivalence study conducted by Eon Labs on its 8.0 mg guanabenz tablet, lot 930402, comparing it to Wyeth Ayerst's Wytensin 8.0 mg tablet has been found to be incomplete by the Division of Bioequivalence.

2. The in vitro dissolution testing conducted on the 8.0 mg strength (lot # 930402) is acceptable.

3.The in vitro dissolution testing conducted on the 4 mg strength (lot # 930802)is acceptable. The formulation for the 4 mg tablet is compositionally proportionl to the 8 mg tablet which underwent a bioequivalence study. However, the waiver of in vivo bioequivalence study requirements can not be granted since the 8 mg study was found to be incomplete.

4. The in vitro dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 1000 ml of deaerated water at 37°C using USP apparatus II paddle at 50 rpm. The test product should meet the following specifications:

> Not less than % of the labelled amount of the drug in the dosage form is dissolved in 60 minutes.

Andre J. Jackson /S/ 4/5/95
Division of Bioequivalence
Review Branch I

RD INITIALLED RMhatre
FT INITIALLED RMhatre /S/

Concur: /S/ Date: 4/10/95
Rabindra Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence

cc: ANDA 74-440 original, HFD-630, HFD-600 (OGD, Hare), HFD-130 (JAllen), HFD-652 (Jackson, Mhatre), Drug File.

AJJ/120894/ntp/WP #74440SDW.D93

Table 4. In Vitro Dissolution Testing

Drug (Generic Name):Guanabenz
Dose Strength:8 mg
ANDA No.:74517
Firm:Eon Labs
Submission Date:June 30, 1994
File Name:74517SDW.693

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: Water Volume:1000 ml
Specifications: % in 60 min
Reference Drug: Wytensin
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 930802 Strength(mg) 4.0			Reference Product Lot # 9910134 Strength(mg) 4.0		
	Mean %	Range	%CV	Mean %	Range	%CV
15	83.6		4.5	78.3		6.2
30	88.0		4.8	92.1		4.9
45	89.4		4.4	95.3		4.7
60	90.7		3.6	97.4		4.7

Table 5. In Vitro Dissolution Testing

Drug (Generic Name):Guanabenz
Dose Strength:8 mg
ANDA No.:74517
Firm:Eon Labs
Submission Date:June 30, 1994
File Name:74517SDW.693

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: Water Volume:1000 ml
Specifications: % in 60 min
Reference Drug: Wytensin
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 930402 Strength(mg) 8.0			Reference Product Lot # 9920413 Strength(mg) 8.0		
	Mean %	Range	%CV	Mean %	Range	%CV
15	77.3		5.6	77.5		11.3
30	84.4		4.7	90.8		6.6
45	86.5		4.5	94.9		4.0
60	87.6		4.7	96.8		2.5

Table 3

GUANABENZ ACETATE STUDY NO. 9316702B
TABLE C3: SUMMARY OF ADVERSE EVENTS

KEY

Treatment (Trt):
A = Eon
B = Wytensin[R]
(Single 16 mg dose)

Duration:
Onset-End
H = Hours
D = Days
(If >24 Hours)

Severity (Sev):
1 = Mild
2 = Moderate
3 = Severe

Action Taken (Act):
1 = None
2 = Subject discontinued
3 = Other (see CRF)

Relationship (Rel):
1 = None
2 = Remote
3 = Possible
4 = Probable

Outcome (Out):
1 = Recovered
2 = AE continuing
3 = Subject lost to follow-up
4 = Other (see CRF)

Sub	Trt	Adverse Event	Onset (Per/Day)	Duration (Times)	Sev	Act	Rel	Out
01	B	Dry mouth	I/1	1030-1400	1	1	4	1
	A	Tiredness	II/1	1000-1600	1	1	4	1
02	A	Sleepiness	I/1	1000-1730	1	1	4	1
	B	Sleepiness	II/1	1000-1630	1	1	4	1
03	A	Tiredness	II/1	1030-1630	1	1	4	1
04	A	Sleepiness	I/1	1000-1730	1	1	4	1
	B	Ringing in ears	II/1	1250-1300	1	1	2	1
	B	Tiredness	II/1	1300-1700	1	1	4	1
05	B	Lightheadedness	I/1	1030-1100	1	1	4	1
06	A	Tiredness	II/1	1045-1330	1	1	4	1
07	A	Weakness	I/1	0930-1900	1	1	4	1
	A	Sleepiness	I/1	0930-1700	1	1	4	1
	B	Dizziness	II/1	1000-1700	1	1	4	1
	B	Drowsiness	II/1	1000-1700	1	1	4	1
08	-	None reported						
09	-	None reported						
10	B	Dizziness	I/1	0930-1030	1	1	4	1
	B	Sleepiness	I/1	0930-1030	1	1	4	1
11	A	Tiredness	I/1	0915-1830	1	1	4	1
	A	Dizziness	I/1	0915-1700	1	1	4	1
	B	Drowsiness	II/1	0945-1900	1	1	4	1
12	B	Dizziness	I/1	0930-1030	1	1	4	1
	B	Sleepiness	I/1	0930-1030	1	1	4	1
	A	Tiredness	II/1	1000-2000	1	1	4	1

GUANABENZ ACETATE STUDY NO. 9316702B
TABLE C3: SUMMARY OF ADVERSE EVENTS

Sub	Trt	Adverse Event	Onset (Per/Day)	Duration (Times)	Sev	Act	Rel	Out
13	-	None reported						
14	B	Lightheadedness	I/1	0930-1500	1	1	4	1
	A	Drowsiness	II/1	1015-0200	1	3	4	1
15	-	None reported						
16	-	None reported						
17	A	Sleepiness	I/1	1000-1830	1	1	4	1
	B	Tiredness	II/1	1000-1700	1	1	4	1
18	A	Sleepiness	I/1	0930-1830	1	3	4	1
	B	Drowsiness	II/1	1015-1100	1	3	4	1
19	A	Tiredness	I/1	1030-1905	1	1	4	1
	A	Nausea	I/1	1030-1400	1	1	2	1
	A	Nausea	I/1	1905-1930	1	1	2	1
	B	Tiredness	II/1	1030-2100	1	1	4	1
	B	Nausea	II/1	1100-0100	1	3	2	1
20	-	None reported						
21	A	Tiredness	I/1	0945-1400	1	1	4	1
22	A	Tiredness	I/1	1020-1400	1	1	4	1
	A	Dizziness	I/1	1100-1400	1	1	4	1
23	B	Tiredness	I/1	1000-2030	1	1	4	1
	B	Dry mouth	I/1	0930-1130	1	1	4	1
	A	Tiredness	II/1	1000-1915	1	1	4	1
	A	Vertigo	II/1	1000-1915	1	1	4	1
	A	Dry mouth	II/1	1000-0800	1	1	4	1
24	A	Sleepiness	I/1	1100-1930	1	1	4	1
	A	Tiredness	I/1	1100-1930	1	1	4	1
	B	Drowsiness	II/1	1030-1900	1	1	4	1
	B	Dry mouth	II/1	1030-2000	1	1	4	1
25	A	Tiredness	II/1	1000-2000	1	1	4	1
26	B	Tiredness	I/1	0930-2300	1	1	4	1
	A	Tiredness	II/1	1030-1930	1	1	4	1
27	B	Tiredness	II/1	1015-1800	1	3	4	1
28	A	Tiredness	II/1	1030-1730	1	3	4	1

Table 4

ANDA-OR
Guanabenz Acetate Tablets, 4 mg and 8 mg

A COMPARISON OF COMPOSITIONS FOR GUANABENZ ACETATE TABLETS 4 MG AND 8 MG

	Guanabenz Acetate 4 mg Tablets		Guanabenz Acetate 8 mg Tablets	
Component	Amount per Tablet	% w/w	Amount per Tablet	% w/w
Guanabenz Acetate, USP (Equivalent to 4 or 8 mg Guanabenz)	mg	8.690	mg	8.690
Anhydrous Lactose, NF	mg	42.759	mg	42.759
Microcrystalline Cellulose, NF	mg	26.034	mg	26.034
Pregelatinized Starch, NF	mg	12.931	mg	12.931
Sodium Starch Glycolate, NF	mg	8.621	mg	8.621
Magnesium Stearate, NF	mg	0.603	mg	0.603
Colloidal Silicon Dioxide, NF	mg	0.259	mg	0.259
FD&C Blue #1 Aluminum Lake	mg	0.060	mg	0.060
Iron Oxide, Dark Brown #33300	mg	0.043	mg	0.043
Totals	mg	100.000	mg	100.000