

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 83972**

**BIOEQUIVALENCE REVIEW(S)**

Hydrochlorothiazide  
25 and 50 mg Tablets  
ANDA 83-972

Barr Laboratories  
Northvale, New Jersey  
AF 42-189  
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REVIEW OF A BIOAVAILABILITY STUDY

1. The objective of the study was to determine the bioavailability of Barr's Hydrochlorothiazide in comparison with Merck's Hydrodiuril, a brand of hydrochlorothiazide, by measuring the unchanged drug excreted in the urine by human subjects. The study was a two-way crossover design employing 22 subjects. The dose was a single 50 mg tablet of the test or the reference drug.
2. The subjects were 21-55 years of age and 135-220 pounds in weight. They were given a medical history and physical examination. The following preclinical laboratory tests were administered: WBC, RBC, HCT, HGB, and differential; calcium, phosphorus, glucose, BUN, LDH, SGOT, uric acid, cholesterol, total bilirubin, alkaline phosphatase, glucose-6-phosphate dehydrogenase and urinalysis. The subjects abstained from medication and alcohol two weeks prior to the initiation of the study. Coffee, tea, and soft drinks were prohibited during the entire study day.
3. On study day 1, one group of eleven subjects received a single oral dose of 50 mg of test drug and the other group of eleven subjects received 50 mg of the reference drug. The subjects ingested the tablet with 120 ml water, and were allowed 120 ml water at each urine collection time. Urine was collected at 0, 1, 2, 3, 4, 6, 8, 12, and 24 hours. All urine specimens were measured for volume and pH, and the unchanged drug determined by the method of Sheppard et. al. After a wash-out period of 7 days the subjects were crossed over.
4. The study report contains the individual and mean urine drug levels, individual and mean cumulative drug excretion data, curves (individual and mean) for urine drug levels and cumulative excretion of the drug, raw data of percent transmittance and optical density, recovery data and standard curve. Analyses of variance of area under the curve, cumulative urine excretion and urine drug levels at each sampling times are submitted.
5. The study was conducted by

COMMENTS:

1. The investigators have demonstrated satisfactorily the specificity, sensitivity, and the linearity of the assay method. The lowest detectable level of hydrochlorothiazide in urine is 2.5 mcg/ml.
2. The comparison of mean values of the area under the urine drug levels curves indicates that the test drug is 94.7% as bioavailable as the reference drug. The important pharmacokinetic parameters for the test and reference drugs are enumerated in table 1:

TABLE 1

PHARMACOKINETIC PARAMETERS OF HYDROCHLOROTHIAZIDE

<u>Parameter</u>	<u>Barr HCT</u>	<u>Hydrodiuril (Merck)</u>
Peak ht; Cmax (mg/hr)	4.82	4.42
Time to Peak (hrs)	3	3
AUC (0-24 hrs), mg	26.44	27.93
Half-life, t 1/2, hrs	4.3	4.8

The differences detectable at a significance level of 0.05 and a power of the test of 0.80 for parameters analyzed are shown below:

TABLE 2

<u>Parameter Analyzed</u>	<u>% Differences Detectable</u>
Area under the curve	20
Peak Heights	30
Cumulative excretion	20

The data in Tables 1 and 2 indicate that the test drug is as bioavailable as the reference drug.

3. The mean values of the cumulative excretion of the drug in the urine are also supportive of the bioequivalence of the two preparations. The test and reference drugs are excreted to the extent of 47.8% and 46.7% in the urine in 24 hours. The individual curves as well as mean curve for cumulative excretion of the drug in 24 hours approach asymptotic values.

4. The in vitro dissolution data on the test and reference drugs also indicates support for the bioequivalence of the two drug products. - In 30 minutes 97.2% of the drug in the Barr tablet is in solution; 94.2% of the drug in the Merck tablet is in solution during the same time. All in all the study was well designed and executed.

5. The amounts of the drug and the excipients for the 25 mg and 50 mg tablets are shown in table 3.

TABLE 3

25 mg and 50 mg Tablet Formulations

<u>Ingredient</u>	<u>25 mg Tablet</u>	<u>50 mg Tablet</u>
Hydrochlorothiazide (2% excess)	25.5 mg	51.0 mg
Avicel		
Lactose USP		
Magnesium Stearate USP		
Starch		
FD&C Yellow		
Purified Water USP QS		

The amounts of drug and the excipients in the 50 mg tablet are an exact duplicate of those in 25 mg tablet.

RECOMMENDATION:

The data from the study clearly indicates that the test and reference drugs are bioequivalent. Approval of the study for both 25 mg and 50 mg tablet formulations is recommended.

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