CENTER FOR DRUG EVALUATION AND RESEARCH

75-273

APPLICATION NUMBER:

BIOEQUIVALENCE

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #75-273 SPONSOR: TEVA Pharmaceuticals
DRUG: Ketoconazole Tablets
DOSAGE FORM: Tablets STRENGTH: 200 mg
REFERENCE PRODUCT: Janssen's Nizoral® Tablets, 200 mg
TYPE OF STUDY: Two single dose studies under fasting conditions
Study Site:
Under Fasting Conditions:
Clinical Facility: MDS Harris, Clinical Research, Phoenix, AZ
Analytical Facility:
NE

Under Non-fasting Conditions:
Clinical Facility: Gateway Medical Research, Inc., St. Charles, MO
Analytical Facility:

STUDY SUMMARY: The single-dose, fasting bioequivalence study (study #19539) and the single-dose non-fasting bioequivalence study (study #B-06117) conducted by TEVA Pharmaceuticals on its Ketoconazole Tablets, 200 mg, comparing it with the reference listed drug Janssen's Nizoral® Tablets, 200 mg, have been found acceptable. Under fasting conditions, the 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX were all within the acceptable range of 80-125%. Under non-fasting conditions, the ratios of the test mean to the reference mean for the AUCT, AUCI, CMAX were within the acceptable range of 0.8-1.25.

DISSOLUTION: The comparative dissolution testing data are acceptable.

PRIMARY REVIEWER: Zakaria Wahba, Ph.D. BRANCH: III
INITIAL: Z.W. DATE: 5/8/98

ACTING GROUP LEADER: Moheb Makary, Ph.D. BRANCH: III
INITIAL: MHM DATE: 5/8/98

ACTING DIRECTOR: Dale P. Conner, Pharm.D.
DIVISION OF BIOEQUIVALENCE
INITIAL: DPC DATE: 5/11/98

DIRECTOR
OFFICE OF GENERIC DRUGS
INITIAL: _____ DATE: _____

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #75-273 SPONSOR: TEVA Pharmaceuticals

DRUG: Ketoconazole Tablets

DOSAGE FORM: Tablets STRENGTH: 200 mg

REFERENCE PRODUCT: Janssen's Nizoral® Tablets, 200 mg

TYPE OF STUDY: Two single dose studies under fasting conditions

Study Site:

Under Fasting Conditions:

Clinical Facility: MDS Harris, Clinical Research, Phoenix, AZ

Analytical Facility:

Under Non-fasting Conditions:

Clinical Facility: Gateway Medical Research, Inc., St. Charles, MO

Analytical Facility:

STUDY SUMMARY: The single-dose, fasting bioequivalence study (study #19539) and the single-dose non-fasting bioequivalence study (study #B-06117) conducted by TEVA Pharmaceuticals on its Ketoconazole Tablets, 200 mg, comparing it with the reference listed drug Janssen's Nizoral® Tablets, 200 mg, have been found acceptable. Under fasting conditions, the 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX were all within the acceptable range of 80-125%. Under non-fasting conditions, the ratios of the test mean to the reference mean for the AUCT, AUCI, CMAX were within the acceptable range of 0.8-1.25.

DISSOLUTION: The comparative dissolution testing data are acceptable.

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DIVISION OF BIOEQUIVALENCE

INITIAL: DPC DATE: 5/11/98

DIRECTOR

OFFICE OF GENERIC DRUGS

INITIAL: _____ DATE: _____

Ketoconazole
200 mg Tablets
ANDA #**75-273**
Reviewer: Z.Z. Wahba
File #75273sw.d97

TEVA Pharmaceuticals USA
Sellersville, PA
Submission Date:
December 12, 1997
March 27,1998

REVIEW OF TWO IN-VIVO BIOEQUIVALENCE STUDIES AND IN VITRO DISSOLUTION TESTING DATA

I. OBJECTIVE:

Review the following:

1. TEVA's in vivo bioequivalence studies under fasting and non-fasting conditions comparing its drug product Ketoconazole Tablets, 200 mg to the reference listed drug Janssen's Nizoral® Tablets, 200 mg.

2. Dissolution data for the test and reference drug products.

II. INTRODUCTION:

Ketoconazole is an antifungal agent used for the treatment of a number of superficial and systemic fungal infections.

Ketoconazole is rapidly absorbed from the GI tract, with peak plasma levels reached within 1 to 2 hours following oral administration. The bioavailability of oral ketoconazole depends on the pH of the gastric contents in the stomach; an increase in the pH results in decreased absorption of the drug. Absorption of ketoconazole is generally improved by food. About 90% of the drug in the circulation is bound to plasma proteins, primarily albumin. Plasma concentrations of ketoconazole appear to decline in a biphasic manner with a half-life of approximately 2 hours in the initial phase and approximately 8 hours in the terminal phase. Ketoconazole is partially metabolized, in the liver, to several inactive metabolites by oxidation and degradation of the imidazole and piperazine rings, by oxidative O-dealkylation, and by aromatic hydroxylation. The major route of elimination of ketoconazole and its metabolites appears to be through the bile into the intestinal tract. About 13% of the dose is excreted in the urine, of which 2 to 4% is unchanged drug.

Ketoconazole is available commercially as Nizoral Tablets, 200 mg,

manufactured by Janssen Pharmaceutica.

III. BIOEQUIVALENCE STUDY UNDER FASTING CONDITION
Clinical Study #19539

A. Sponsor:
TEVA Pharmaceuticals USA
650 Cathill Road
Sellersville, PA 18960-0630

Study Site:
Clinical Facility
MDS Harris
Clinical Research
Phoenix, Arizona

Analytical Facility

[redacted]

Investigator:
Clinical Investigator: Irving E. Weston, M.D.

Clinical Study Dates:
Period I: May 22-24, 1997
Period II: May 29-31, 1997

B. Study design:
Single dose, randomized, two-way crossover study under fasting conditions.

C. Subjects:
Twenty-six (26) healthy male subjects were recruited and 25 subjects completed the study. The subjects were within 20 to 47 years of age, and their body weights were within ± 15% of the ideal weight as defined by the Metropolitan Life Insurance Chart.

D. Food and Fluid Intake:
Subjects fasted for at least 10 hours (overnight) before dosing and 4 hours after dosing. The drug products were

administered with 240 mL tap water. The subjects received their medication according to a randomized dosing schedule. Standard meals were provided at appropriate times thereafter (at 4 and 9.5 hours after drug administration).

E. Treatment Plan:

Test product: 1 X 200 mg Ketoconazole Tablets (TEVA), Lot #0554-094, Batch size: tablets, potency: 100.4%, content uniformity: 100.1%, manufacturing date: 12/18/1996.

Reference product: 1 X 200 mg Nizoral® Tablets (Janssen), Lot #95G344E, potency: 101.3%, content uniformity: 100.1%, expiration date: 06/01/1999.

Washout period: 7 days.

F. Blood Sampling:

Blood samples (10 mL each) were collected in vacutainers, before dosing (0 hour) and at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 24.0, 36.0 and 48.0 hours post-dosing. The plasma samples were separated, collected and stored frozen at -20°C until analysis.

G. Assay Methodology:

1. Methods:
The plasma assay of ketoconazole was performed by

detection.

The assay validation data are summarized as follows:

2. Linearity: 0.04 to 8.0 μg/mL.

3. Sensitivity:
The lower limit of quantitation was 0.04 μg/mL for ketoconazole in human plasma. Samples with assayed values below 0.04 μg/mL were reported as zero.

5. Study Validation : (pp #229-230, Vol. C1.2)
Results are summarized in the following two tables.

Overall Precision and Accuracy for Quality Control Samples

Theoretical Conc. μg/mL	0.125	0.800	6.000
Mean Con.	0.125	0.840	6.156
Precision (%CV)	8.00	9.40	7.00
Accuracy (%) (% of change)	0.00	5.00	7.00
n	30	30	30

Calibration Standards Summary

Theoretical Conc. ug/mL	0.04	0.05	0.1	0.25	0.5	1.00	2.00	4.00	7.00	8.00
Mean Con.	0.039	0.049	0.102	0.245	0.517	1.011	1.991	3.967	7.022	7.996
Precision (%CV)	7.69	8.16	7.84	4.49	3.29	5.04	5.52	5.12	4.53	4.05
Accuracy (%) (% of change)	-2.5	-2.0	2.0	-2.0	3.40	1.10	-0.45	-0.82	0.31	-0.05
n	15	15	15	13	14	14	15	15	15	13

5. Recovery:
The mean recovery for ketoconazole from plasma was 86.7%, 95.9% and 93.9% at concentrations of 0.04 μg/mL, 0.5 μg/mL and 8.0 μg/mL, respectively.

6. Stability:
   1. Ketoconazole was stable at room temperature and during 3 freeze/thaw cycles.

   2. Long term stability data showed that ketoconazole was stable for at least 5 years at -20 °C.

H. In Vivo BE Study and Statistical Analysis:
Twenty-six (26) healthy male subjects were recruited. Subjects #18 did not show up for the study. Subject #22 exhibited abnormally low ketoconazole concentrations following administration of the reference product for unknown reasons.

The subjects that were included in the statistical analysis are subjects #1-17, 19-21 and 23-26.

Adverse Events: There were 14 reported adverse events. None of the adverse events was considered serious.

The pharmacokinetic parameters of ketoconazole were analyzed using SAS-GLM procedure for analysis of variance. The pharmacokinetic parameters for the plasma ketoconazole concentrations, as well as the following parameters, AUCt, AUCi, Cmax, Tmax, Kel, T1/2 are summarized in the Tables below:

Table #1
Mean Plasma Concentrations (μg/mL)
of Ketoconazole in 24 Subjects Following a Single Oral Dose of 200 mg Ketoconazole Tablet Under Fasting Conditions
(Test Lot #0554-094, Reference Lot #95G344E)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	0.14	0.20	0.20	0.29	0.70
0.67	1.62	1.37	1.69	1.42	0.96
1	2.80	1.63	2.67	1.53	1.05
1.33	3.24	1.46	3.32	1.58	0.98
1.67	3.53	1.38	3.49	1.51	1.01
2	3.68	1.22	3.70	1.44	0.99
2.5	3.52	1.21	3.48	1.10	1.01
3	3.27	1.05	3.30	1.11	0.99
4	2.69	0.99	2.59	1.01	1.04
6	1.31	0.64	1.23	0.60	1.07
8	0.75	0.43	0.69	0.42	1.09
12	0.22	0.20	0.20	0.17	1.10
24	0.01	0.03	0.01	0.02	1.00
36	0.00	0.00	0.00	0.00	.
48	0.00	0.00	0.00	0.00	.

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio

Table #2
Mean Pharmacokinetic Parameters (Arithmetic) in 24 Subjects Following a Single Oral Dose of 200 mg Ketoconazole Tablet Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	20.20	7.48	20.21	6.88	1.00
AUCT	19.77	7.46	19.81	6.92	1.00
CMAX	4.17	1.39	4.32	1.16	0.96
KE	0.35	0.12	0.34	0.12	1.02
*LAUCI	18.23	0.55	19.00	0.38	0.96
*LAUCT	17.79	0.56	18.56	0.38	0.96
*LCMAX	3.89	0.42	4.17	0.28	0.93
THALF	2.27	0.87	2.32	0.89	0.98
TMAX	2.05	0.96	2.04	0.63	1.01

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio

UNIT: AUC=μG.HR/ML CMAX=μG/ML

* The values represent the geometric means (antilog of the means of the logs).

Table #3
LSMeans And The 90% Confidence Intervals in 24 Subjects Following a Single Oral Dose of 200 mg Ketoconazole Tablet Under Fasting Conditions

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCI	18.16	19.00	0.96	84.81	107.73
LAUCT	17.72	18.57	0.95	84.53	107.74
LCMAX	3.89	4.16	0.94	83.25	105.02

UNIT: AUC=μG.HR/ML CMAX=μG/ML

Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R

Comments on the BE study: The mean plasma ketoconazole levels for the test and reference products were comparable to each other as shown in Table #1 and Figure #1. The 90% confidence intervals for the LSMeans log-transformed AUCt, AUCi and Cmax were within the acceptable range of 80-125% (Table #3).

NOTE: Subject #22 exhibited abnormally low ketoconazole concentrations following administration of the reference product. Subject #22 pharmacokinetic parametrs are shown below:

	AUCt (μg/mL)	AUCi (μg/mL)	Cmax (μg/mL)
Reference Treatment	0.8637	1.036	0.203
Test-Treatment	17.55	17.86	3.539

LSMeans And The 90% Confidence Intervals in 25 Subjects (All Subjects Including Subject #22) Following a Single Oral Dose of 200 mg Ketoconazole Tablet Under Fasting Conditions

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCI	18.18	16.83	1.08	85.72	136.18
LAUCT	17.75	16.34	1.09	85.25	138.42
LCMAX	3.87	3.67	1.06	84.04	132.55

UNIT: AUC=μG.HR/ML CMAX=μG/ML
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R

The subject was asked to return to the clinic and he repeated both of the study periods (8/16/97 and 8/23/97). The pharmacokinetic parameters for subject #22 after redose are shown below:

	AUCt (μg/mL)	AUCi (μg/mL)	Cmax (μg/mL)
Reference Treatment	23.45	25.12	4.49
Test-Treatment	21.18	21.66	5.67

The ketoconazole concentrations observed for this subject for the redose study periods were within the range observed for the other subjects who originaly completed the study. The redose results indicate that the original results for subject #22 were aberrant. Therefore, it is justified to exclude subject #22 from the original analysis.

IV. SINGLE DOSE BIOEQUIVALENCE STUDY, UNDER NON-FASTING CONDITIONS (Study #B-06117)

A. Sponsor:

TEVA Pharmaceuticals USA
650 Cathill Road
Sellersville, PA 18960-0630

Clinical Facility

Gateway Medical Research, Inc.

116 North Main Street
St. Charles, MO 63301

Analytical Facility

Inc.

Statistical Facility

Investigator:
Clinical Investigator: Irwin Plisco, M.D.

Clinical Study Dates:
Period I: July 01, 1997
Period II: July 08, 1997
Period III: July 15, 1997

B. **Study design:**
Randomized, three-way, three-treatment, three-period, six-sequence, single dose crossover study, under fasting and non-fasting conditions.

C. **Subjects:**
Eighteen (18) healthy male subjects but 17 subjects completed the study. The subjects were within 19 to 42 years of age, and their body weights were within ± 15% of the ideal weight as defined by the Metropolitan Life Insurance Chart.

D. **Treatment Plan:**
Treatment A: Fasting conditions, 1 X 200 mg Ketoconazole Tablets (TEVA), Lot #0554-094, Batch size tablets, potency: 100.4%, content uniformity: 100.1%, manufacturing date: 12/18/1996.

Treatment B: Non-fasting condition, 1 X 200 mg Ketoconazole Tablets (TEVA), Lot #0554-094, Batch size: tablets, potency: 100.4%, content uniformity: 100.1%, manufacturing date: 12/18/1996.

Treatment C: **Non-fasting conditions**, 1 X 200 mg Nizoral® Tablets (Janssen), Lot #95G344E, potency: 101.3%, content uniformity: 100.1%, expiration date: 06/01/1999.

Washout period: 7 days.

E. Drug, Food and Fluid Intake:

Subjects who received treatment A fasted overnight for 10.5 hours before dosing and for 4 hours after each drug administration. Subjects who received treatments B and C fasted overnight for 10 hours before they were fed a standard high fat breakfast, which was consumed in its entirety 30 minutes before drug administration. Each dose was followed by 240 mL of room temperature tap water according to randomized dosing schedule. Standard meals were provided at appropriate times thereafter (lunch at 4 hours, supper at 9 hours post-dose).

F. Blood sampling:

Blood samples (10 mL each) were collected in vacutainers, before dosing (0 hour) and at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 24.0, 36.0 and 48.0 hours post-dosing. The plasma samples were separated, collected and stored frozen at -20°C until analysis.

G. Assay Methodology:

1. Methods:

The plasma assay of ketoconazole was performed by

The assay validation data are summarized as follows:

2. Linearity: 50.0 to 5000 ng/mL.

3. Sensitivity:

The lower limit of quantitation was 50.0 ng/mL for ketoconazole in human plasma. Samples with assayed values below 50.0 ng/mL were reported as zero.

5. Study Validation :

Results are summarized in the following two tables.

Overall Precision and Accuracy for Quality Control Samples

Theoretical Conc. ng/mL	100	700	3500
Mean Con.	100	762	3449
Precision (%CV)	6.0	4.8	2.8
Accuracy (%) (% of change)	0.0	9.0	-1.5
n	18	17	18

Calibration Standards Summary

Theoretical Conc. ng/mL	50	100	200	500	1000	2000	3000	5000
Mean Con.	45.9	96.0	207	504	1047	2124	3054	4772
Precision (%CV)	5.7	5.2	3.8	2.9	1.5	2.1	2.3	1.8
Accuracy (%) (% of change)	-8.2	-4.0	4.0	1.0	5.0	6.0	2.0	-4.6
n	9	9	9	9	9	9	9	9

5. Recovery:
The mean recovery for ketoconazole from plasma was 71.1%, 75.0% and 78.7% at concentrations of 100 ng/mL, 700 ng/mL and 3500 ng/mL, respectively.

6. Stability:
   1. Ketoconazole was stable at room temperature and during 3 freeze/thaw cycles.

   2. Long term stability data showed that ketoconazole was stable for at least 207 days at -20 °C.

H. Data Analysis:
Eighteen (18) healthy male subjects but 17 subjects completed the study (subjects #1-15 and 17-18). Subject #16 was unable to participate in Period-2 because of transportation problems.

Adverse Events: There were no adverse events reported during this study.

The pharmacokinetic parameters of ketoconazole were analyzed using SAS-GLM procedure for analysis of variance. The pharmacokinetic parameters for the plasma ketoconazole concentrations, as well as the following parameters, AUCt, AUCi, Cmax, Tmax, Kel, T1/2 are summarized in the Tables below:

Table #4
Mean Plasma Concentrations (ng/mL)
of ketoconazole in 17 Subjects Following a Single Oral Dose of 200 mg ketoconazole Tablet Under Non-Fasting Conditions
(Test Lot #)0554-094, Reference Lot #95G344E)

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.00	0.00	0.00	0.00	0.00	0.00	.
0.33	189.52	267.13	53.78	137.66	25.11	45.28	3.52
0.67	1750.24	977.03	363.30	512.25	220.00	302.91	4.82
1	2864.41	1067.94	926.51	927.43	706.18	724.17	3.09
1.33	3203.47	1014.46	1664.48	1369.81	1374.86	943.39	1.92
1.67	3226.76	987.77	2199.71	1461.34	2015.71	918.90	1.47
2	3132.53	937.00	2524.29	1121.65	2435.65	944.50	1.24
2.5	2832.00	931.65	2848.53	809.08	2720.53	723.41	0.99
3	2519.65	934.59	2875.94	709.70	2773.29	587.28	0.88
4	1844.29	743.13	2381.24	814.35	2542.65	810.18	0.77
6	772.82	397.06	1097.65	569.60	1265.12	661.45	0.70
8	382.47	227.47	522.65	328.13	641.35	417.73	0.73
12	89.79	61.60	129.46	113.73	179.91	143.10	0.69
24	12.36	28.18	25.59	38.70	15.49	29.24	0.48
36	0.00	0.00	0.00	0.00	3.42	13.25	.
48	0.00	0.00	0.00	0.00	0.00	0.00	.

(CONTINUED)

	RMEAN13	RMEAN23
TIME HR		
0	.	.
0.33	7.55	2.14
0.67	7.96	1.65
1	4.06	1.31
1.33	2.33	1.21
1.67	1.60	1.09
2	1.29	1.04
2.5	1.04	1.05
3	0.91	1.04
4	0.73	0.94
6	0.61	0.87
8	0.60	0.81
12	0.50	0.72
24	0.80	1.65
36	0.00	0.00
48	.	.

MEAN1=Test-Fast MEAN2=Test.-Fed MEAN3=Ref.-Fed
RMEAN23=T/R ratio under non-fasting conditions
* The values represent the geometric mean (antilog of the means of the logs).

Table #5
Mean Pharmacokinetic Parameters (Arithmetic) for Ketoconazole in 17 Subjects Following a Single Oral Dose of 200 mg Ketoconazole Tablet, Under Non-Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	15331.13	4380.41	14803.80	5132.15	15474.94	4774.99	1.04
AUCT	14135.88	4782.38	14482.35	4786.73	15042.12	4508.97	0.98
CMAX	3485.29	990.36	3319.41	875.98	3176.47	662.93	1.05
KE	0.39	0.09	0.36	0.13	0.33	0.10	1.10
*LAUCI	14725.12	0.30	14010.75	0.34	14810.19	0.30	1.05
*LAUCT	13339.94	0.36	13775.80	0.33	14432.01	0.30	0.97
*LCMAX	3332.48	0.32	3210.89	0.27	3115.82	0.20	1.04
THALF	1.86	0.52	2.23	0.92	2.40	1.06	0.83
TMAX	1.67	0.59	2.43	0.89	2.85	0.72	0.69

(CONTINUED)

	RMEAN13	RMEAN23
PARAMETER		
AUCI	0.99	0.96
AUCT	0.94	0.96
CMAX	1.10	1.05
KE	1.19	1.08
*LAUCI	0.99	0.95
*LAUCT	0.92	0.95
*LCMAX	1.07	1.03
THALF	0.78	0.93
TMAX	0.58	0.85

MEAN1=Test-Fast MEAN2=Test.-Fed MEAN3=Ref.-Fed
UNIT: AUC=μG.HR/ML CMAX=μG/ML
RMEAN23=T/R ratio under non-fasting conditions
* The values represent the geometric mean (antilog of the means of the logs).

Comments on the BE study: Under non-fasting conditions, the mean plasma ketoconazole levels for the test and reference products were comparable to each other as shown in Table #4 and Figure #2. The T/R mean ratios (RMEAN2/3) for log-transformed AUCt, AUCi and Cmax were within the acceptable range of 0.80 to 1.25 (Table #5).

V. FORMULATION

TEVA's formulation for its test product, ketoconazole Tablets,

200 mg is summarized in the following Table.

Formulation

Ingredient	Ketoconazole Tablet, 200 mg	
	mg/Tablet	%
Ketoconazole	200.0	
Lactose Monohydrate	6	9
Corn Starch,	)	.3
Povidone	)	4
Silicon Dioxide,		( )
Microcrystalline Cellulose,	)	2
Magnesium Stearate,		( )
Purified Water	*	
Total	0	.0

*Processing Solvent, Non-residual

VI. IN VITRO DISSOLUTION TESTING

The firm's comparative dissolution testing of the test and reference products is summarized below.

Apparatus:	2 (Paddle) at 50 rpm
Medium & Volume:	0.1 N HCl; 900 mL
Sampling Time:	5, 10, 15, 30 and 45 minutes
Number of Units:	12 Tablets
Tolerances:	The firm's specification is NLT 80%(Q) of the labeled amount of ketoconazole in the dosage form is dissolved in 30 minutes.

The dissolution testing results are shown in the following table.

I. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #0554-094 Strength(mg) 200			Reference Product Lot #95G344E Strength(mg)200		
	Mean %	Range	%CV	Mean %	Range	%CV
5	40.8		10.0	40.4		10.3
10	78.2		7.5	73.3		7.3
15	95.6		2.3	87.2		5.4
30	98.6		0.8	95.0		2.1
45	98.8	[illegible]	0.6	95.9		1.6

VII. AN IMPORTANT COMMENT (it should not be released under FOI)

1. Based on the Division of Bioequivalence Director's letter dated August 05, 1996; in response to Sidmak Laboratories, the dissolution specifications for ketoconazole tablets were presented as the following:

Apparatus:	USP Paddle at 50-75 rpm
Medium & Volume:	0.1 N HCl; 900 mL
Sampling Time:	15, 30, 45, 60 minutes or until 85% mean dissolution is achieved.
Tolerances:	To be established (the Office will review the firm's proposals and will make the recommendations accordingly).

2. The dissolution data for the test and reference listed products are acceptable.

VIII. GENERAL COMMENTS:

1. The single-dose, fasting bioequivalence study (study #19539) and the single-dose non-fasting bioequivalence study (study #B-06117) conducted by TEVA Pharmaceuticals on its Ketoconazole Tablets, 200 mg, comparing it with the reference listed drug Janssen's Nizoral® Tablets, 200 mg, have been found acceptable. Under fasting conditions, the 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX were all within the acceptable range of 80-125%. Under

non-fasting conditions, the ratios of the test mean to the reference mean for the AUCT, AUCI, CMAX were within the acceptable range of 0.8-1.25.

2. The dissolution testing data have met the FDA dissolution requirements.

IX. RECOMMENDATION

1. The two in vivo bioequivalence studies, single-dose under fasting (study #19539) and non-fasting (study #B-06117) conditions, conducted by TEVA Pharmaceuticals on its Ketoconazole Tablet, 200 mg, lot #0554-094, comparing it to the reference listed drug Janssen's Nizoral® Tablets, 200 mg, lot #95G344E, have been found to be acceptable to the Division of Bioequivalence. The two studies demonstrate that under fasting and non-fasting conditions, TEVA's Ketoconazole Tablets, 200 mg, are bioequivalent to Janssen's Nizoral® Tablets, 200 mg.

2. The dissolution testing conducted by the firm on its Ketoconazole Tablets, 200 mg has been found acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.1N HCl as the dissolution medium with apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

The firm should be informed of the above recommendations.

Zakaria Z. Wahba

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED MMAKARY
FT INITIALLED MMAKARY Mohib H. Makary

Concur: Dale P. Conner Date: 5/11/98
Dale P. Conner, Pharm.D.

Director
Division of Bioequivalence