CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-971

BIOEQUIVALENCE

4.1

Ketoconazole ~~Tablets~~ USP, 200 mg
ANDA#74-971
Reviewer: Hoainhon Nguyen
WP#74971s.798

Novopharm Ltd.
Ontario, Canada
Submission Date:
~~July 21~~, 1998
May - 26

Review of a 'Redosing' Study

1. Background:

In order to resolve the question of whether to omit Subjects #4 and 10 from the original single-dose, fasting bioequivalence study (Protocol No. 1552-1), the firm was recommended in the last letter dated October 17, 1997 by the Division of Bioequivalence to redose the above subjects, along with several other 'control' subjects. The firm has completed the 'redosing' study and now submitted the results of the study in the current amendment.

In the original fasting study, there were four subjects (Nos. 4, 5, 10 and 19) that had very low plasma ketoconazole levels in one (but not both) dosing period. Subjects Nos 4 and 10 had low levels after dosing with the reference product, while subjects Nos. 5 and 19 had low levels after dosing with the test product. The relative differences were greater between dosing periods for subjects Nos. 4 and 10 than for Nos. 5 and 19 (The firm utilized a statistical outlier test called "Lund's Test" to qualify subjects Nos. 4 and 10 as "outlier subjects".). Subjects #4 and 10 were entered in the 'redosing' study together with 'control' Subjects #5, 16, 24 and 25 who also participated in the last fasting study and were without the unusual plasma levels of the drug.

2. 'Redosing' Study (Protocol 1960): A Two-Way Single-Dose Open-Label Fasting Bioavailability Study of Ketoconazole 200 mg Tablets and Nizoral® 200 mg Tablets in Six (6) Normal Healthy Non-Smoking Male Volunteers

Study Objective:

The purpose of this study is to confirm the status of two (2) subjects as outliers in Study No. 1552-1. This study design, like the design for Study No. 1552-1,

compared the rate and extent of absorption of ketoconazole 200 mg tablets (Novopharm) against Nizoral® 200 mg tablets (Janssen) under fasting conditions.

Study Investigators and Facilities:

The study was conducted at the bioavailability center of between February 28, 1998 and March 9, 1998. The principal investigator was Paul Y. Tam, M.D.. Plasma samples were assayed by under the supervision of r, between April 10 and 22, 1998.

Demographics:

Six normal, healthy, non-smoking male volunteers between 20-43 years of age, and within 10% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a two-treatment, two-period, randomized crossover study. The subjects were selected previously for the Study No. 1552-1 on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' height and weight ranged 65 - 72 in. and 134 - 189 lbs., respectively. The so-called 'control' subjects were chosen due to their willingness and availability for participation in the redosing study.

Inclusion/exclusion criteria/Restrictions:

Same as in Study No. 1552-1.

Treatments and Sampling:

The two treatments consisted of a single 200 mg dose of either the test product or reference product taken orally with 240 ml of water, under fasting conditions.

Treatment A(Test Product): Novopharm's Ketoconazole tablets, 200 mg, lot # 3040PD (Same as in Study No. 1552-1, batch size of nits, potency of 100.0%).

Treatment B(Reference Product): Janssen's Nizoral® Tablets, 200 mg, lot #

94E303A (~~Same~~ as in Study No. 1552-1, potency of 102.7%).

Blood samples were collected at predose, 0.25, 0.50, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 6, 8, 12 and 24 hours following drug administration. Blood samples were cooled in an ice bath and then centrifuged under refrigeration. The plasma was separated and stored at -25°C until assayed.

Assay Methodology: The analytical method was developed and validated by . Ketoconazole and the internal standard were assayed using a method, with liquid-liquid phase extraction, and detection, in the same method as in Study No. 1552-1.

Assay Specificity:

The method is specific for ketoconazole with no significant interference seen at the retention time of the drug or internal standard in chromatograms of blank plasma standards and predose subject samples.

Linearity:

(Based on actual study standard curves)

The assay was linear in the range of 50.0 to 5000 ng/ml.

Reproducibility:

(Based on actual study quality controls)

Interday CV's were: 3.1% at 3500 ng/ml, 2.3% at 700 ng/ml and 2.7% at 100 ng/ml.

Sensitivity:

(Based on actual study back-calculated standard data)

Sensitivity limit was 50.0 ng/ml (CV% = 4.0). Any level below this limit was reported as zero.

Prestudy validation data showed CV% for LOQ of 5.0 ng/ml (n=6) was 5.8.

Accuracy:

(Based on actual study quality controls)

Percent recovery of control samples were: 102% at 3500 ng/ml, 105% at 700 ng/ml and 95.2% at 100 ng/ml.

Stability:

Freeze-thaw (three-cycle) stability, room-temperature (24-hour) stability and processed-sample (48-hour) stability of plasma samples was demonstrated adequately in **a pre-study validation study** using control samples of 3500, 700 and 100 ng/ml concentrations. Long-term stability of 207 days was also reported with the mean change for ketoconazole over the studied period was -3.7%, -2.7% and +5.0% for the 3500, 700 and 100 ng/mL concentrations, respectively.

The stability studies are acceptable.

Pharmacokinetic Results:

AUC(0-T) was calculated using the trapezoidal method. AUC(0-Infinity) was calculated by : AUC(0-Infinity) = AUC(0-T) + [last measured concentration/ KEL]. CMAX and TMAX were observed values of the peak plasma concentration and time to peak plasma concentration, respectively. KEL and T1/2 were calculated from the terminal portion of the log concentration versus time curve.

The results of the redosing study are given below.

KETOCONAZOLE 200 MG TABLET FASTING STUDY
NOVOPHARM 1960
ANDA # 74-971
STATISTICAL SUMMARY

RESULTS OF SUPPLEMENTAL STUDY 1960 AND ORIGINAL STUDY 1552-1

SUPPLEMENTAL STUDY 1960 ORIGANAL STUDY 1552-1

AUCTLQC

SUB	TEST AUCT	REF AUCT	T/R RATIO	SUB	TEST AUCT	REF AUCT	T/R RATIO
1	24790	10966	2.26	10	20365	2027	10.05
2	17327	16898	1.03	4	16440	1080	15.22
3	18964	16918	1.12	24	23957	9349	2.56
4	16646	21581	0.77	25	14353	23634	0.61
5	9517	10181	0.93	5	2765	13117	0.21
6	17188	16117	1.07	16	19003	18474	1.03

AUCINF

SUB	TEST AUCI	REF AUCI	T/R RATIO	SUB	TEST AUCI	REF AUCI	T/R RATIO
1	26364	11679	2.26	10	20865	2382	8.76
2	17461	17311	1.01	4	16554	1178	14.05
3	19504	17569	1.11	24	14892	9696	1.54
4	17195	22039	0.78	25	24893	23926	1.04
5	9843	10526	0.94	5	2902	13930	0.21
6	17933	16968	1.06	16	19147	18613	1.03

CMAX

SUB	TEST CMAX	REF CMAX	T/R RATIO	SUB	TEST CMAX	REF CMAX	T/R RATIO
1	4941	1605	3.08	10	4447	296	15.02
2	4838	5152	0.94	4	4788	706	6.78
3	3866	3800	1.02	24	4456	2597	1.72
4	4281	4839	0.88	25	4785	5837	0.82
5	3324	3556	0.93	5	1144	3448	0.33
6	4684	4526	1.03	16	4483	4623	0.97

As concluded by the firm, *'The large differences between products that were observed for Subject #10 (Subject #1 in current study) and Subject #4 (Subject #2 in current study) in the original study (Study 1552-1) were not seen in this study (Study 1960) as illustrated in the above table. The differences between products for the control subjects were either closer or not much different than those seen in the original study.' and 'The conclusion from this study is that Subject #4 and Subject #10 from the original study are not from a subpopulation that has low levels after dosing with the reference product and high levels after dosing with the test product. There is no indication that there is such subpopulation. The aberrant values observed for Subject #4 (and possibly for Subject #10) from the original study were most likely due to subject non-compliance. Therefore, the data for Subject #4 and Subject #10 in the original study should not be included in the statistical evaluation for bioequivalence.'*

Adverse Events: There was no adverse event reported by any subject in this redosing study.

3. DBE's Comment on the Results of the Redosing Study:

The reviewer agrees with the conclusion by the firm above. Based on the data provided in the redosing study, the exclusion of Subjects #4 and 10 from the statistical analysis of the original fasting study, Study No. 1552-1, is now considered **acceptable**.

The final statistical analysis for the original fasting study, Study No. 1552-1, is based on 37 data sets. The results of this study are given below.

4. Results of Fasting Study (Protocol No. 1552-1) With Exclusion of Subjects #4 and 10:

There was a significant difference (alpha=0.05) between treatments for TMAX(p=0.0112). There was no significant differences between treatments for other analyzed parameters.

Table I

Ketoconazole Comparative Pbarmacokinetic Parameter

Fasting Study; Dose= 200 mg; n = 37

(With Subjects #4 and 10 excluded)

Parameters	Novopharm's Mean (CV)	Nizoral® Mean (CV)	90% C.I.	Ratio T/R
AUC (0-T) ng.hr/ml	16732*	16788*	[0.88;1.13]	1.00
AUC (0-Inf) ng.hr/ml	17156*	17369*	[0.87;1.12]	0.99
CMAX(ng/ml)	4170.4*	4103.8*	[0.91;1.14]	1.02
TMAX (hrs)	1.36(43)	1.71(36)		
KEL (1/hrs)	0.410(24)	0.426(22)		
T1/2 (hrs)	1.84(39)	1.74(32)		

*Geometric LSMeans

Table II

Comparative Mean Plasma Levels of Ketoconazole, ng/mL(CV)

Fasting Study; Dose = 200 mg; n = 37

(With Subjects #4 and 10 excluded)

Hour	Novopharm's	Nizoral®
0	0	0
0.25	192.5(139)	117.0(260)
0.50	2273(63)	1305(84)
0.75	3557(42)	2627(52)
1.00	3984(42)	3329(42)
1.25	3995(40)	3688(36)
1.50	3997(40)	3818(32)
1.75	3895(36)	3839(30)
2.00	3770(34)	3745(29)
2.33	3590(34)	3579(31)
2.67	3361(34)	3535(32)
3.00	3095(33)	3194(32)
3.50	2687(36)	2817(34)
4.00	2424(40)	2534(36)
6.00	1136(51)	1155(53)
8.00	545.8(66)	523.5(74)
12.00	116.2(126)	96.84(161)
24.00	7.589(370)	4.330(433)
$AUC(0\text{-}T)_{ng.hr/ml}$	18870(40)	18067(39)
$AUC(0\text{-}Inf)_{ng.hr/ml}$	19244(40)	18628(38)
CMAX	4544.5(34)	4260.9(28)

Adverse Effects:

There were only two mild adverse events, pallor and diaphoresis, which were reported by Subject No. 39 during the test treatment, and judged not related to the treatment.

5. DBE's Comments on Fasting Study (Study No. 1552-1):

1. The redosing study is acceptable. The results of this study demonstrate that the aberrant values observed for Subjects #4 and 10 in the original fasting, single-dose study are not due to the existence of a subpopulation or the test product failure.

2. The fasting, single-dose study results as summarized above are considered acceptable. The test product is shown to be equivalent to the reference product in the extent and rate of absorption as measured by log-transformed AUCs and CMAX, under fasting conditions.

6. Recommendations:

1. The single-dose, fasting bioequivalence study (Protocol No. 1552-1) conducted by Novopharm Ltd. on its test product, Ketoconazole Tablets, 200 mg, lot # 3040PD, comparing it with the reference product, Nizoral[R] Tablets, 200 mg, lot # 94E303A, has been found **acceptable** by the Division of Bioequivalence. The study demonstrates that Novopharm's Ketoconazole Tablets, 200 mg, is bioequivalent to Janssen's Nizoral Tablets, 200 mg, under fasting conditions.

2. The single-dose, non-fasting bioequivalence study conducted by Novopharm Ltd. on its test product, Ketoconazole Tablets, 200 mg, lot # 3040PD, comparing it with the reference product, Nizoral[R] Tablets, 200 mg, lot # 94E303A, has been found **acceptable** by the Division of Bioequivalence. The study demonstrates that Novopharm's Ketoconazole Tablets, 200 mg, is bioequivalent to Janssen's Nizoral Tablets, 200 mg, under non-fasting conditions. (Recommendation No. 2 from the review of the submission dated May 16, 1997)

3. The in-vitro dissolution testing conducted by Novopharm Ltd. on its Ketoconazole Tablets, 200 mg, and Janssen's Nizoral Tablets, 200 mg, has been found acceptable.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of 0.1 N H Cl at 37°C using USP XXIII apparatus II(paddle) at 50 rpm. The

test product should meet the following specifications:

Not less than 80% of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

(Recommendation No. 3 from the review of the submission dated May 16, 1997)

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 8/6/98

Concur: 8/6/98
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

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OCT - 3 1997

Ketoconazole Tablets USP, 200 mg
ANDA # 74-971
Reviewer: Hoainhon Nguyen
WP #74971a.597

Novopharm Ltd.
Ontario, Canada
Submission Date:
May 16, 1997

Review of a Study Amendment

The firm has submitted a study amendment in response to the Division of Bioequivalence's Deficiency Comments issued in the letter dated March 10, 1997. The Deficiency Comments, the firm's summarized Responses and the DBE's Comments on the firm's Responses are given below.

Deficiency Comment 1: *"The fasting bioequivalence study (Protocol No. 1552-1) for the test product is not acceptable. The 90% confidence intervals for log-transformed AUC(0-T), AUC(0-Inf) and CMAX are outside the acceptable limit of [0.80;1.25]. Data from Subjects Nos. 4 and 10 should not be excluded from the data analyses "solely on the basis of a statistical test", and the firm "should provide scientific evidence or explanations to justify the exclusion of the subjects' data from statistical analysis", according to the Guidance of Statistical Procedures for Bioequivalence Studies (issued by the Division of Bioequivalence July 1, 1992). As indicated in the final report, there were no noted clinical anomalies with any of these subjects, and the chromatography was consistent for both dosing periods for each subject."*

Firm's Response 1:

In the absence of "scientific evidence or explanations" for the low plasma levels of the drug in Subjects 4 and 10 during Reference treatments, the firm argued that the reference product failure must have been the reason, and the exclusion of these subjects' data is justified: *"It is clear that the reference product is the source of the problem with respect to the low drug plasma levels obtained for subjects 4 and 10."* and *"What remains is the possibility that the reference product, in the case of these two subjects, was either subpotent or the drug in these tablets was not bioavailable."*

DBE's Comment: In addition to the possibility of "product failure", there is also the possibility of existence of a "subpopulation" for which low plasma levels of the

drug may be observed.

According to the Guidances *Statistical Procedures for Bioequivalence Studies* (issued by the Division of Bioequivalence July 1, 1992), *"The existence of an outlier could be indicative of the following problems with interchangeability of two formulations:*

1. Product failure: a subject obtained an unusually high or low response to one or the other of the products because of a problem with the specific dosage unit(s) administered. Examples include a sustained/modified release dosage form exhibiting dose dumping or a dosage unit whose coating inhibited dissolution.

2. Subpopulation: a subject may be representative of a type of subject, present in the general population in low numbers, for whom the relative bioavailability of the two products is markedly different than it is for the majority of the population, and for whom the two products are not bioequivalent, even though they might be bioequivalent in the majority of the population.

*In the case of product failure, it may make a difference whether the unusual response is observed on the test product or the reference product. In the case of a subpopulation, however, **even if the unusual response is observed on the reference product**, there may still be concern for lack of interchangeability of the two products."*

Since the possibility of existence of a "subpopulation" can not be ruled out based on the data on hand, the exclusion of the "outlier" subjects from the statistical analysis is not completely justified.

The firm may consider, if possible, **redosing the same "outlier" subjects** to confirm or to eliminate the possibility of existence of a "subpopulation". These subjects should be redosed with other "control" subjects, who also participated in the study previously and were without the unusual plasma levels of the drug. If the same "outlier" subjects no longer exhibit the unusually low plasma levels, then the possibility of "product failure" may be confirmed, and the exclusion of data from these subjects may be accepted.

Deficiency Comment 2: *"The single-dose, non-fasting bioequivalence study conducted by Novopharm Ltd. on its test product, Ketoconazole Tablets, 200 mg, lot # 3040PD, comparing it with the reference product, Nizoral[R] Tablets, 200 mg, lot # 94E303A, has been found incomplete. The long-term stability study for the Non-Fasting study is deficient in demonstraing that the plasma samples were stable for the entire sample storage duration of 69 days. The long-term stability study only covered a 64-day period."*

Firm's Response 2: The firm submitted the long-term stability data for ketoconazole in -20°C freezer for 207 days. Percent change of ketoconazole in three control concentrations, 3500 ng/ml, 700 ng/ml and 100 ng/ml, was -3.7, -2.7 and 5.0, respectively (mean change of six replicates per control concentration).

DBE's Comment: The long-term stability data are acceptable.

Deficiency Comment 3: *"The in-vitro dissolution testing conducted by Novopharm Ltd. on its Ketoconazole Tablets, 200 mg, has been found incomplete due to the reason cited in Deficiency No. 3. The dissolution specification should include the actual sampling time of the dissolution testing (e.g., 30 minutes, 40 minutes or 50 minutes ...). It is recommended, based on the dissolution data submitted, that the specification should be dissolved in 30 minutes."*

Firm's Response 3: The firm revised the in-house dissolution procedure to include the sampling time of 30 minutes, and the specification to be dissolved in 30 minutes" as recommended by DBE.

DBE's Comment: The firm's response is adequate.

Recommendation:

1. The single-dose, fasting bioequivalence study (Protocol No. 1552-1) conducted by Novopharm Ltd. on its test product, Ketoconazole Tablets, 200 mg, lot # 3040PD, comparing it with the reference product, Nizoral[R] Tablets, 200 mg, lot # 94E303A, has been found **incomplete** by the Division of Bioequivalence due to the reason cited in the DBE Comment No. 1 above. The exclusion of the Subjects

#4 and 10 is found not completely justified.

2. The single-dose, non-fasting bioequivalence study conducted by Novopharm Ltd. on its test product, Ketoconazole Tablets, 200 mg, lot # 3040PD, comparing it with the reference product, Nizoral[R] Tablets, 200 mg, lot # 94E303A, has been found **acceptable** by the Division of Bioequivalence. The study demonstrates that Novopharm's Ketoconazole Tablets, 200 mg, is bioequivalent to Janssen's Nizoral Tablets, 200 mg, under non-fasting conditions.

3. The in-vitro dissolution testing conducted by Novopharm Ltd. on its Ketoconazole Tablets, 200 mg, and Janssen's Nizoral Tablets, 200 mg, has been found acceptable.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of 0.1 N H Cl at 37°C using USP XXIII apparatus II(paddle) at 50 rpm. The test product should meet the following specifications:

[illegible]

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 10/5/97

Concur: _____ Date: 10/3/97
Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

c. File,

FEB 28 1997

Ketoconazole Tablets, USP
200 mg
ANDA # 74-971
Reviewer: Hoainhon Nguyen
WP # 74971sd-996

Novopharm Ltd.
Stouffville, Ontario, Canada
Submission Date:
September 30, 1996
December 6, 1996
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Review of Bioequivalence Studies and Dissolution Data

I. Background:

Ketoconazole is a synthetic broad-spectrum antifungal agent used in the treatment of the following systemic fungal infections: candidiasis, blastomycosis, coccidioidomycosis, and for the treatment of patients with severe recalcitrant cutaneous dermatophyte infections who have not responded to topical therapy or oral griseofulvin, or who are unable to take griseofulvin. Ketoconazole presumably exerts its antifungal activity by altering cellular membranes, resulting in increased membrane permeability, secondary metabolic effects, and growth inhibition. Ketoconazole is practically insoluble in water but soluble in acids, and has pK_as of 2.9 and 6.5.

Ketoconazole is rapidly absorbed from the GI tract, with peak plasma levels reached within 1 to 2 hours following oral administration. Ketoconazole is dissolved in gastric secretions and converted to the hydrochloride salt prior to absorption from the stomach. 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. The effect of food on the rate and extent of GI absorption of the drug has not been clearly determined. Food generally increases absorption of ketoconazole by increasing the rate and/or extent of dissolution of ketoconazole (e.g., by increasing bile secretions) or by delaying stomach emptying. Considerable interindividual variations in CMAX and AUCs have been reported with a specific oral dose of ketoconazole. In one cross-over study in adults who received single oral doses of ketoconazole of 100 mg, 200 mg and 400 mg, a comparison of dose versus AUC suggested that ketoconazole undergoes saturable first pass elimination since bioavailability of the lower dose was relatively poor.

Ketoconazole is 84-99% bound to plasma proteins, primarily albumin. Plasma concentrations of ketozonazole 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 ketoconazle 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.

Adverse effects associated with ketoconzole include nausea and/or vomiting, abdominal pain, pruritus, headache, dizziness, somnolence, fever and chills, photophobia, diarrhea, gynecomastia, impotence, thrombocytopenia, leukopenia, hemolytic anemia, and bulging fontanelles.

Ketoconazole is available commercially as Nizoral Tablets, 200 mg, manufactured by Janssen Pharmaceutica.

The firm has submitted the results of a fasting, single-dose bioequivalence study and a non-fasting, single-dose bioequivalence study, both comparing its Ketaconazole Tablets, 200 mg, with Janssen's Nizoral Tablets, 200mg. Comparative dissolution data for both products are also submitted.

II. Bioequivalence Study:

A. Fasting Study (Protocol No. 1552-1): A Two-Way Single-Dose Open-Label Fasting Bioavailability Study of Ketoconazole 200 mg Tablets in Normal Healthy Non-Smoking Male Volunteers

Study Objective:

The purpose of this study is to evaluate the bioequivalency of Novopharm's ketoconazole tablets, 200 mg, and Janssen's Nizoral® Tablets, 200 mg, under fasting conditions.

Study Investigators and Facilities:

The study was conducted at [redacted] between June 8, 1996 and June 16, 1996. The

principal investigator was . Plasma samples were assayed by under the supervision of between June 21, 1996 and July 25, 1996.

Demographics:

Thirty-nine normal, healthy, non-smoking male volunteers between 18-41 years of age, and within 10% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a two treatment, two period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 121 - 228 lbs and 65 - 76 in., respectively.

Inclusion criteria:

Subjects especially did not have any history or presence of: cardiac, pulmonary, gastrointestinal, endocrine, neuromuscular, neurological, hematological, liver or kidney disease, diabetes, epilepsy, glaucoma or any condition known to interfere with the absorption, distribution, metabolism or excretion of drugs, hypersensitivity to ketoconazole or related drugs, asthma, chronic bronchitis or other bronchospastic condition, inflammatory diseases of the gastrointestinal tract, such as peptic ulcer, regional enteritis or ulcerative colitis, regular use of medication, abuse of alcoholic beverages, or use of enzyme-inducing and enzyme-inhibiting drugs such as phenobarbital, carbamazepine and cimetidine within 30 days prior to entry into the study.

Restrictions:

They were free of all medications at least 14 days prior to each study period and allowed no concomitant medications during the study sessions. No alcohol and no xanthine-containing products were allowed 48 hours prior to each drug administration. The subjects fasted for 10 hours prior to and 4.5 hours after each drug administration. The washout duration between the two phases was one week. Duration of confinement was 10 hours pre-dose to approximately 24 hours post-dose in each period.

Treatments and Sampling:

The two treatments each consisted of a single 200 mg dose of either the test product or reference product taken orally with 240 ml of water.

Test Product: Novopharm's Ketoconazole tablets, 200 mg, lot # 3040PD (Batch size of units, potency of 101.1%).

Reference product: Janssen's Nizoral® Tablets, 200 mg, lot # 94E303A (Potency of 102.4%).

Blood samples were collected at predose, 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.33, 2.67, 3.0, 3.5, 4.0, 6.0, 8.0, 12.0, and 24.0 hours following drug administration. Blood samples were centrifuged under refrigeration and the plasma was separated and immediately stored at -20°C pending assay.

Assay Methodology:

The analytical method was developed and validated by . Ketoconazole and the internal standard were assayed using a nethod, with liquid-liquid phase extraction, and letection.

Assay Specificity:

The method is specific for ketoconazole with no significant interference seen at the retention time of the drug or internal standard in chromatograms of blank plasma standards and predose subject samples.

Linearity:

(Based on actual study standard curves)

The assay was linear in the range of 50.0 to 5000 ng/ml.

Reproducibility:

(Based on actual study quality controls)

Interday CV's were: 4.6% at 3500 ng/ml, 5.8% at 700 ng/ml and 5.3% at

100 ng/ml.

Sensitivity:

(Based ~~on~~ actual study back-calculated standard data)

Sensitivity limit was 50.0 ng/ml (CV% = 9.8). Any level below this limit was reported as zero.

Prestudy validation data showed CV% for LOQ of 5.0 ng/ml (n=6) was 5.8.

Accuracy:

(Based on actual study quality controls)

Percent recovery of control samples were: 105% at 3500 ng/ml, 110% at 700 ng/ml and 100% at 100 ng/ml.

Stability:

Freeze-thaw (three-cycle) stability, room-temperature (24-hour) stability and processed-sample (48-hour) stability of plasma samples was demonstrated adequately in **a pre-study validation study** using control samples of 3500, 700 and 100 ng/ml concentrations. Long-term stability of 42 days (during the Fasting Study) and 64 days (during the Non-Fasting Study) for control samples stored with study subject samples was also reported.

The stability studies are acceptable.

Pharmacokinetic Results:

AUC(0-T) was calculated using the trapezoidal method. AUC(0-Infinity) was calculated by : AUC(0-Infinity) = AUC(0-T) + [last measured concentration/ KEL]. CMAX and TMAX were observed values of the peak plasma concentration and time to peak plasma concentration, respectively. KEL and T1/2 were calculated from the terminal portion of the log concentration versus time curve.

Statistical Analyses:

Analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatment, subjects within sequence, and days of administration for the above pharmacokinetic parameters as well as for the plasma concentrations at each sampling time. The 90% confidence intervals for AUC's, CMAX, lnAUC's and lnCMAX were calculated, based on least squares means, using the two, one-sided t-test.

Results:

All thirty-nine enrolled volunteers completed the clinical portion of the study. The statistical analysis was performed using 39 data sets.

There were significant differences (alpha=0.05) between treatments for CMAX (p=0.0446). There was no significant difference between treatments for other analyzed parameters. Four subjects (Nos. 4, 5, 10 and 19) had very low plasma ketoconazole levels in one (but not both) dosing period. Subjects Nos 4 and 10 had low levels after dosing with the reference product, while subjects Nos. 5 and 19 had low levels after dosing with the test product. The relative differences were greater between dosing periods for subjects Nos. 4 and 10 than for Nos. 5 and 19. The firm utilized a statistical outlier test called "Lund's Test" to qualify subjects Nos. 4 and 10 as "outlier subjects". However, **"there were no noted clinical anomalies with any of these subjects, and the chromatography was consistent for both dosing periods for each subject."**

The study results summarized in the tables below are based on the data for all subjects:

Table I

Ketoconazole Comparative Pharmacokinetic Parameters

Fasting Study; Dose = 200 mg; n = 39

Parameters	Novopharm's Mean (CV)	Nizoral[R] Mean (CV)	90% C.I.	Ratio T/R
AUC (0-T) ng.hr/ml	16946*	14901*	[0.93;1.39]	1.14
AUC (0-Inf) ng.hr/ml	17364*	15485*	[0.92;1.36]	1.12
CMAX(ng/ml)	4213.4*	3683.7*	[0.96;1.37]	1.14
TMAX (hrs)	1.36(43)	1.69(36)		
KEL (1/hrs)	0.409(24)	0.429(25)		
T1/2 (hrs)	1.84(38)	1.74(33)		

*Geometric LSMeans

Table II

Comparative Mean Plasma Levels of Ketoconazole, ng/ml(CV)

Fasting Study; Dose = 200 mg; n = 39

Hour	Novopharm's	Nizoral[R]
0	0	0
0.25	187.1(140)	111.0(268)
0.50	2294(61)	1244(88)
0.75	3576(44)	2510(57)
1.00	4010(41)	3183(47)
1.25	4022(39)	3520(42)
1.50	4012(38)	3642(38)
1.75	3925(35)	3660(37)
2.00	3775(34)	3569(37)
2.33	3588(33)	3409(39)
2.67	3355(33)	3365(39)
3.00	3094(32)	3041(39)
3.50	2674(35)	2680(41)
4.00	2412(39)	2411(43)
6.00	1130(50)	1099(58)
8.00	542.3(66)	498.5(78)
12.00	115.9(124)	91.88(166)
24.00	7.200(381)	6.349(356)
AUC(0-T)ng.hr/ml	18846(39)	17220(45)
AUC(0-Inf)ng.hr/ml	19216(39)	17764(44)
CMAX	4548(33)	4068(35)

Adverse Effects:

There were only two mild adverse events, pallor and diaphoresis, which were reported by Subject No. 39 during the test treatment, and judged not related to the treatment.

B. Non-Fasting Study (Protocol No. 1776): A Three-Way Single-Dose Open-Label Food-Effect Bioavailability Study of Ketoconazole 200 mg Tablets in

Normal Healthy Non-Smoking Male Volunteers

Study Objective:

The purpose of this study is to determine the effect of food on the bioequivalence of ketoconazole 200 mg tablets relative to Nizoral 200 mg tablets.

Study Investigators and Facilities:

The study was conducted at [redacted] between September 5, 1996 and September 19, 1996. The principal investigator was Paul Y. Tam, M.D.. Plasma samples were assayed by [redacted] under the supervision of [redacted] between October 5, 1996 and November 14, 1996.

Demographics:

Twenty-four normal, healthy, non-smoking male volunteers between 19-42 years of age, and within 10% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a three-treatment, three-period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 126 - 214 lbs and 65 - 77 in., respectively.

The subjects were randomly assigned to one of three treatments during each study period according to one of six sequences.

Inclusion criteria and Restrictions:

Same as in Protocol No. 1552-1 for the Fasting Study above except that during the non-fasting legs of the study the subjects were given a standard high-fat content breakfast 30 minutes prior to drug administration. The breakfast consisted of one fried egg, one buttered English muffin, one slice of American cheese, one slice of Canadian bacon, one serving of hash brown potatoes, 8 fluid ounces of whole milk and 6 fluid ounces of orange juice.

Treatments and Sampling:

The three treatments each consisted of a single 200 mg dose of either the test product or reference product taken orally with 240 ml of water under fasting or non-fasting conditions.

Test Product: Novopharm's Ketoconazole tablets, 200 mg, lot # 3040PD (Batch size of units, potency of 101.1%), taken either following an overnight fast (Treatment C) or five minutes after completing a standard high-fat content breakfast (Treatment A).

Reference product: Janssen's Nizoral® Tablets, 200 mg, lot # 94E303A (Potency of 102.4%), taken five minutes after completing a standard high-fat content breakfast (Treatment B).

Blood samples were collected at predose, 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.33, 2.67, 3.0, 3.5, 4.0, 6.0, 8.0, 12.0, and 24.0 hours following drug administration. Blood samples were centrifuged under refrigeration and the plasma was separated and immediately stored at -20°C pending assay.

Assay Methodology:

The analytical method was developed and validated by Ketoconazole and the internal standard were assayed using a method, with liquid-liquid phase extraction, and letection.

Assay Specificity:

The method is specific for ketoconazole with no significant interference seen at the retention time of the drug or internal standard in chromatograms of blank plasma standards and predose subject samples.

Linearity:

(Based on actual study standard curves)

The assay was linear in the range of 50.0 to 5000 ng/ml.

Reproducibility:

(Based on actual study quality controls)

Interday CV's were: 6.4% at 3500 ng/ml, 6.4% at 700 ng/ml and 5.4% at 100 ng/ml.

Sensitivity:

(Based on actual study back-calculated standard data)

Sensitivity limit was 50.0 ng/ml (CV% = 7.3). Any level below this limit was reported as zero.

Prestudy validation data showed CV% for LOQ of 5.0 ng/ml (n=6) was 5.8.

Accuracy:

(Based on actual study quality controls)

Percent recovery of control samples were: 90.9% at 3500 ng/ml, 97.7% at 700 ng/ml and 102% at 100 ng/ml.

Stability:

See under Assay Methodology for the Fasting Study. The long-term stability study only covered a freezer storage period of 64 days while the duration between the first sample collection (September 5, 1996) and the last sample analysis (November 14, 1996) was 69 days. The long-term stability study therefore is **not adequate**.

Pharmacokinetic Results:

AUC(0-T) was calculated using the trapezoidal method. AUC(0-Infinity) was calculated by : AUC(0-Infinity) = AUC(0-T) + [last measured concentration/ KEL]. CMAX and TMAX were observed values of the peak plasma concentration and time to peak plasma concentration, respectively. KEL and T1/2 were calculated from the terminal portion of the log concentration versus time curve.

Statistical Analyses:

Analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatment, subjects within sequence, and ~~days~~ of administration for the above pharmacokinetic parameters as well as for the plasma concentrations at each sampling time. The 90% confidence intervals for AUC's, CMAX, lnAUC's and lnCMAX were calculated, based on least squares means, using the two, one-sided t-test.

Results:

Twenty-three of 24 enrolled volunteers completed the clinical portion of the study. The statistical analysis was performed using 23 data sets.

There were significant differences (alpha=0.05) between treatments for CMAX (p=0.0092) and TMAX(p=0.0001). There was no significant difference between treatments for other analyzed parameters. The study results are summarized in the tables below:

Table III

Ketoconazole Comparative Pharmacokinetic Parameters

Non-Fasting Study: Dose = 200 mg; n = 23

Parameters	Test(fed) Mean (CV)	Nizoral(fed) Mean (CV)	Test(fasted) Mean(CV)	90% C.I. (T_{fed} vs R_{fed})	Ratio T_{fed}/R_{fed}
AUC (0-T) ng.hr/ml	13749*	13218*	14483*	[0.92;1.18]	1.04
AUC (0-Inf) ng.hr/ml	14225*	13626*	14862*	[0.92;1.18]	1.04
CMAX ng/ml	3067.3*	3063.5*	3539.3*	[0.88;1.14]	1.00
TMAX hrs	2.55(26)	2.42(28)	1.87(25)		
KEL 1/hrs	0.394(22)	0.392(23)	0.389(21)		
T1/2 hrs	1.84(22)	1.88(27)	1.87(25)		

*Geometric LSMeans

Table IV

Comparative Mean Plasma Levels of Ketoconazole, ng/ml(CV)

Non-Fasting Study; Dose = 200 mg; n = 23

Hour	Novopharm's(fed)	Nizoral(fed)	Novopharm's(fasted)
0	0	0	
0.25	15.45(204)	41.18(241)	209.3(189)
0.50	269.3(114)	393.8(194)	1703(87)
0.75	841.6(98)	748.6(132)	2797(55)
1.00	1483(80)	1239(95)	3255(44)
1.25	2032(61)	1777(53)	3376(40)
1.50	2416(45)	2337(43)	3443(39)
1.75	2593(32)	2642(39)	3443(33)
2.00	2719(29)	2790(32)	3380(32)
2.33	2897(28)	2904(30)	3147(33)
2.67	2853(27)	2844(28)	2877(30)
3.00	2858(30)	2740(30)	2694(31)
3.50	2736(31)	2530(33)	2393(32)
4.00	2413(32)	2268(35)	2087(35)
6.00	1117(42)	1095(48)	947.5(48)
8.00	545.0(56)	504.2(64)	447.9(62)
12.00	130.3(90)	127.7(91)	120.8(103)
24.00	0	2.604(480)	2.443(480)
$AUC(0\text{-}T)_{ng.hr/ml}$	14734(32)	14264(34)	16042(39)
$AUC(0\text{-}Inf)_{ng.hr/m}$	15249(32)	14687(34)	16416(39)
CMAX	3244(31)	3259(32)	3858(32)

Adverse Effects:

There were three mild to moderate adverse events, lightheadedness, pallor and headache, which were reported by Subject No. 23 during the test (fasted) treatment, and judged not related to the treatment.

III. Dissolution Testing:

Drug (Generic Name): Ketoconazole Tablets Firm: Novopharm
Dose Strength: 200 mg ANDA # 74-971
Submission Date: September 30, 1996

Table - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:
USP XXIII Basket __ Paddle X RPM 50 No. Units Tested: 12
Medium: 0.1N HCl Volume: 900 ml
Reference Drug: (Manuf.) Nizoral[R]; Janssen
Assay Methodology: _____

II. Results of In-Vitro Dissolution Testing:

Sampling Times (min)	Test Product Lot # 3040PD Strength (mg) 200			Reference Product Lot # 94E303A Strength (mg) 200		
	Mean % Dissolved	Range	(CV%)	Mean % Dissolved	Range	(CV%)
10	92.7		(9.6)	61.5		(12.4)
20	98.4		(3.4)	89.7		(7.0)
30	99.7		(1.1)	94.8		(2.8)
40	100.2		(0.86)	96.9		(1.5)
50	99.9		(0.90)	97.3		(1.4)
60	100.0		(1.1)	97.8		(1.2)

Firm's Specification:
NLT 75% in 45min

IV. Deficiencies:

1. The fasting bioequivalence study (Protocol No. 1552-1) for the test product is **not acceptable.** The 90% confidence intervals for log-transformed AUC(0-T), AUC(0-Inf) and CMAX are outside the acceptable limit of [0.80;1.25]. Data from Subjects Nos. 4 and 10 should not be excluded from the data analyses "solely on the basis of a statistical test", and the firm "should provide scientific evidence or explanations to justify the exclusion of the subjects data from statistical analysis", according to the Guidance of Statistical Procedures for Bioequivalence Studies (issued by the Division of Bioequivalence July 1, 1992). As indicated in the final report, there were no noted clinical anomalies with any of these subjects, and the chromatography was consistent for both dosing periods for each subject.

2. The long-term stability study for the Non-Fasting study is deficient in demonstraing that the plasma samples were stable for the entire sample storage duration of 69 days. The long-term stability study only covered a 64-day period.

3. The dissolution specification should include the actual sampling time of the dissolution testing (e.g., 30 minutes, 40 minutes or 50 minutes ...). It is recommended, based on the dissolution data submitted, that the specification should be tes.

V. Recommendations:

1. The single-dose, fasting bioequivalence study (Protocol No. 1552-1) conducted by on its test product, Ketoconazole Tablets, 200 mg, lot # 3040PD, comparing it with the reference product, Nizoral® Tablets, 200 mg, lot # 94E303A, has been found **unacceptable** by the Division of Bioequivalence due to the reason cited in Deficiency No. 1 above.

2. The single-dose, non-fasting bioequivalence study conducted by on its test product, Ketoconazole Tablets, 200 mg, lot # 3040PD, comparing it with the reference product, Nizoral® Tablets, 200 mg, lot # 94E303A, has been found **incomplete** by the Division of Bioequivalence due to the reason cited in Deficiency No. 2.

3. The in-vitro dissolution testing conducted by on its Ketoconazole Tablets, 200 mg, has been found incomplete due to the reason cited in Deficiency No. 3.

The firm should be informed of the Deficiencies.

/S/

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

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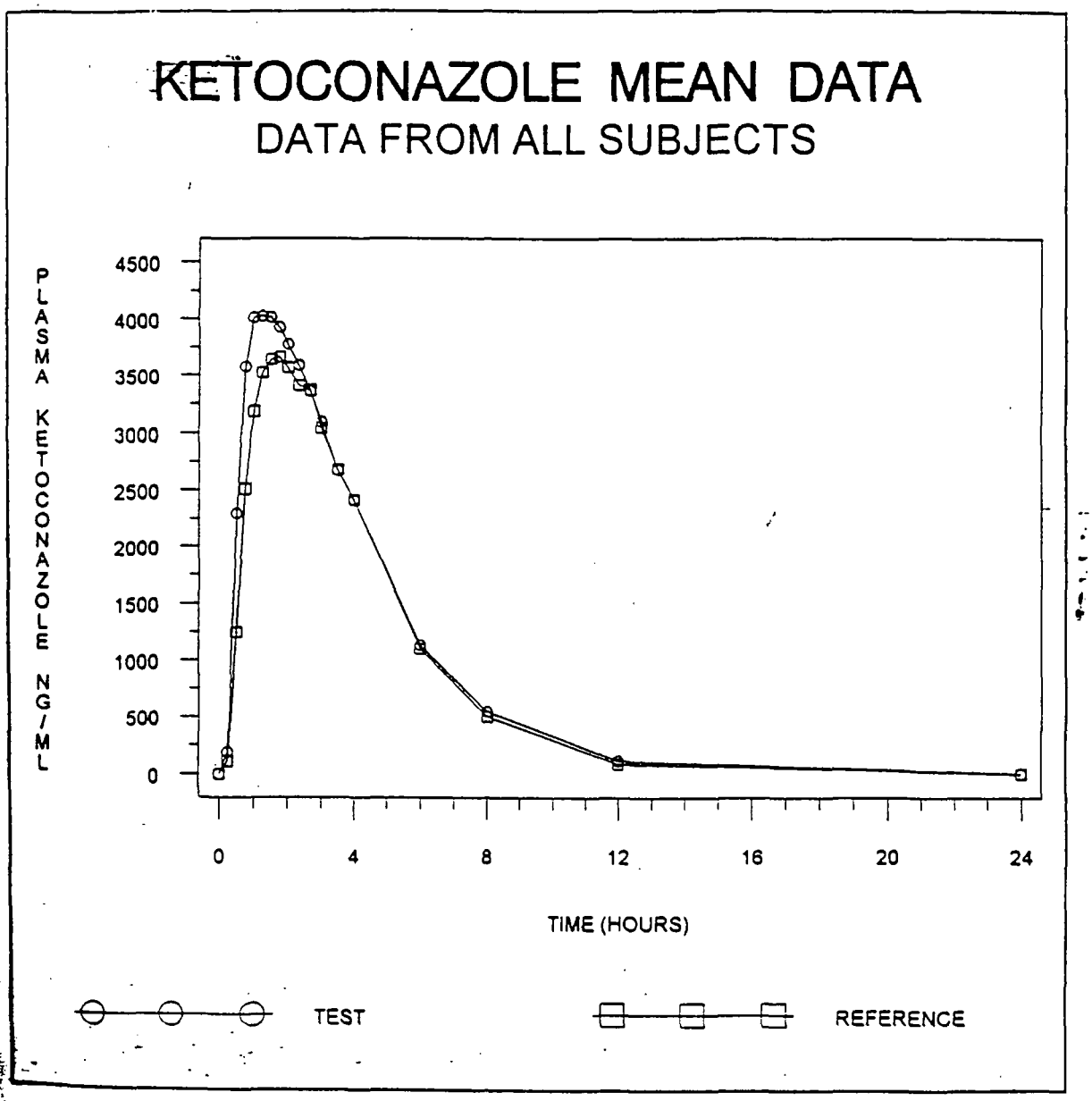
FT INITIALED YHUANG /S/ 6/97

Yes note: USP requires dissolution test.

NP # 74971sd. 996 Attachment 1 of 3



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