CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-310

MEDICAL REVIEW(S)

Date of Review Initiation: October 18, 1993

Clinical Review of NDA 20-310

Original Submission

Sponsor: Johnson and Johnson Consumer Products, Inc.
Skillman, N.J. 08558

Drug: Ketoconazole Shampoo, 1%

Date of Submission: December 18, 1992 was the date the NDA was originally submitted. The following amendments have been submitted since that date:

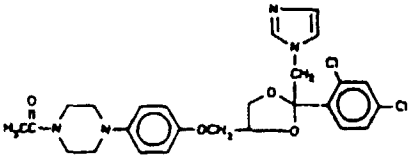
- January 26, 1993. Chemistry amendment.
- February 4, 1993. Formulation amendment.
- February 10, 1993. Formulation amendment.
- March 3, 1993. Statistical amendment.
- March 22, 1993. Chemistry amendment.
- March 23, 1993. Clinical amendment (justifies splitting the six-center study into two three-center studies).
- April 2, 1993. Statistical amendment.
- April 7, 1993. Statistical amendment.
- April 19, 1993. Four-month safety update.
- May 3, 1993. Microbiology amendment.
- May 4, 1993. Chemistry amendment.
- May 27, 1993. Request for teleconference.
- June 8, 1993. Agenda for teleconference.
- July 9, 1993. Clinical amendment (page which was missing from original submission).
- September 22, 1993. (not available to reviewers)
- September 29, 1993. Chemistry amendment.
- October 1, 1993. Chemistry amendment.
- October 25, 1993. Chemistry amendment.
- October 29, 1993. Clinical amendment (submission of irritation study).
- November 8, 1993. Clinical amendment (submission of gender analysis).

NDA: 20-310

Formulation:

Component	% w/w
Ketoconazole, USP	1.000
Carbomer 1342, NF	
Sodium Laureth Sulfate	
Sodium *Cocoyl* Sarcosinate	
Cocamide MEA	
Glycol Distearate	
BHT	
Tetrasodium EDTA	
Fragrance	
Polyquaternium-7	
Quaternium-15	
FD&C Blue No. 1	
Sodium Hydroxide, NF	
Sodium Chloride	
Purified Water, USP	
Hydrochloric Acid, NF	
**	Sufficient to adjust pH to 7.0-7.43 (not to exceed 0.3% w/w total).
***	Sufficient to adjust viscosity to 4,000-9,000 cps. (not exceed 0.6% w/w total).
****	Sufficient to adjust pH to 7.0-7.3

Ketoconazole is a member of the imidazole class of antifungal drugs, with the following chemical structure:



Proposed Indication: "Controls the flaking, scaling and itching associated with dandruff". The product is proposed for OTC marketing.

Directions for use: "Wet hair. Apply sufficient shampoo to produce a generous lather. Gently massage over entire scalp area. Rinse and repeat. Use regularly, at least twice a week".

Packaging: Eleven fluid ounce and one fluid ounce plastic bottles.

Related Submission: The studies in this NDA were performed under IND Nizoral (ketoconazole) Shampoo, 2% has been approved for prescription sale in the U.S. since 1990. This NDA (19-927) is held by Janssen Pharmaceutica. Ketoconazole is also marketed as a topical 2% cream for the treatment of topical fungal infections and in 200 mg. tablets for the treatment of systemic fungal infections. The approved indication for the 2% shampoo is "the reduction of scaling due to dandruff".

The use of systemic ketoconazole has been associated with hepatotoxicity.

Other Reviews:

A. Chemistry Review: In her review dated May 18, 1993, Dr. Tso, the chemist, found deficiencies in a number of areas, including manufacturing methodology, stability, container information, etc.

B. Pharmacology Review: In his review dated January 4, 1993, Dr. Joshi, the pharmacologist did not object to the approval of the application. He did question whether a product in Pregnancy Category "C" should be marketed OTC.

C. Biopharmaceutics Review: In her review signed May 10, 1993, Dr. Ajayi, the biopharmaceuticist, did not object the approval of this application. However, she did state that the product should not be labeled for OTC use in children below 12 years of age due to lack of absorption data in this group.

D. Microbiology Review: This is not yet available.

E. Statistical Review: This is not yet available.

Background: As noted above, this product is intended for OTC use. It is one-half the strength of the approved prescription ketoconazole shampoo. The 2% shampoo is approved for marketing in many foreign countries. The 1% shampoo (manufactured by Janssen Pharmaceutica) is approved for OTC marketing in Argentina, Mexico and Thailand, and for prescription marketing in Colombia.

This NDA was originally under the review of Dr. Ramzy Labib. In his preliminary (unwritten) review, Dr. Labib found that the human irritation study submitted in support of the NDA was deficient. The sponsor agreed to perform a new study and submit the results to us. These results will be presented at the end of this review.

A comment on the OTC use of an antifungal drug in the control of dandruff may be appropriate.

The most widely used OTC anti-dandruff active ingredients are not commonly classified as anti-fungals (e.g., zinc pyrithione, selenium sulfide, etc.). Dandruff is generally defined as a condition involving increased shedding from the scalp of dead skin cells. No specific organism has ever been identified as the primary cause of dandruff, although some literature suggests that Pityrosporum ovale, a yeast - like fungus, is often associated with dandruff. This is sufficient rationale to justify exposure to the target populace to topical antifungal drugs with low systemic absorption.

Material Reviewed: In general, two conditions must be met in order to justify the switch of a prescription drug product to OTC status. The first is that the disease to be treated must be easily diagnosed by the layperson. Since there are many products on the OTC market for dandruff and FDA has published a monograph for products intended to treat this disorder, this condition has been met.

The second condition to be met for the OTC market is that the product must be reasonably safe. That is, there must be evidence that removing the use of the drug from the supervision of a physician does not unduly expose the user to risks to his health in terms of adverse reactions, including systemic toxicity.

The greatest theoretical risk from a topical ketoconazole product is likely to be systemic absorption and possible subsequent toxicity. The FDA biopharmaceutics reviewer found that while absorption through the skin from either 1% or 2% ketoconazole shampoos has not been demonstrated, it has not conclusively been ruled out. Due to reports of minimal systemic absorption from a 2% cream formulation in infants, she recommended that use of the 1% shampoo not be permitted in children under 12 years of age.

The sponsor has submitted the following studies in support of this application:

1. Phase I safety studies using the marketed Nizoral Shampoo (2% ketoconazole). These studies were found inadequate on their face by Dr. Labib and are replaced by studies using the 1% formulation proposed for marketing (described in Part B of this review).

2. Single-center dose ranging study comparing 0.3%, 1.0% and 2.0% ketoconazole shampoos with vehicle.

3. Single-center open-label long-term safety study of 1% ketoconazole shampoo.

4. Multi-center comparison of 1% ketoconazole shampoo to vehicle in subjects with moderately severe dandruff.

5. Single-center study comparing the 1% ketoconzole shampoo used in earlier studies to one made by a new production method.

Other sections which will be included in this review are:

1. Review of safety update (including review of adverse reaction reports for Nizoral Shampoo).
2. Summary of safety information.
3. Labeling review.
4. Conclusions and recommendations.

A. Controlled and Uncontrolled Clinical Studies

1. Study Title: A Placebo-Controlled, Randomized, Double-Blind, Noncrossover Evaluation of the Dose-Related Efficacy of Ketoconazole Shampoo (0.3%, 1% and 2%) in the Treatment of Moderate to Severe Dandruff. (J&J Protocol No. 16399.41)

Investigator: I. Kantor, M.D.
Research Testing Laboratories, Inc.
Great Neck, N.Y. 11021

Method:

a. Study Design: This was a single-center, double-blind, randomized, parallel group study comparing the safety, and effectiveness of ketoconazole shampoo (0.3%, 1%, 2%) to vehicle.

b. Patient Selection: Patients of either sex, 18 years of age and older were entered into the study. The patients were to have moderate to severe dandruff as defined by a combined baseline score of at least 7 (of a possible 10) for combined adherent and loose dandruff. The maximum score for either one of the parameters was 5, and it was necessary that the adherent dandruff score be at least 3. (See scale of dandruff severities under Effectiveness Parameters, below). The patients were not to use any other anti-dandruff medications during the cause of the study.

c. Patient Exclusion: The following list of exclusions is taken directly from the sponsor's submission:

- Active dermatological conditions which can involve the scalp (eg, psoriasis, seborrheic dermatitis, eczema, ichthyosis, etc.).
- History of unusual reactions to skin care toiletry products or cosmetics, or sensitivity to any of the test article components.
- Requirement for chronic medication (eg, insulin, antihistamines, corticosteroids, topical steroids, etc.) that might influence the outcome of the study.
- Requirement for systemic therapy or local treatment of dandruff or seborrheic dermatitis during the study or within two weeks prior to the start of the study.
- Atopic dermatitis and/or severe atopic dermatological background.
- A concurrent disease that might prevent the subject from completing the study.
- Pregnant (as determined by interview) or lactating females.
- Participation in any other local clinical study within three weeks of entering this study or during the period required to complete this study.

Subjects were also excluded from the study if they did not complete the two-week pre-study washout period.

d. Dosage and Duration of Treatment: Patients were instructed to shampoo with Prell (non-medicated) Shampoo exclusively for 2 weeks prior to treatment initiation. Subjects were then randomized to one of the four treatment groups using

stratification for age, sex, and baseline dandruff rating. They were instructed to shampoo twice weekly at home for 8 weeks. The study days designated for shampooing were 3, 7, 10, 14, 17, 21, 24, 28, 31, 35, 38, 42, 45, 49, and 52. The subjects were instructed to use about 15 mL of shampoo or vehicle, lather, rinse, and repeat. The subjects were instructed then to again use Prell exclusively during the 2 week period following the test period.

e. Effectiveness Parameters: The patients returned for evaluation at weeks 2, 4, 6, 8 and 10 (two week follow-up evaluation). The following parameters were evaluated:

Dandruff: Loose and adherent types of dandruff were separately scored by the investigator (dermatologist) according to the following scale:

0	=	No dandruff
1	=	Almost no dandruff (very slight)
2	=	Mild dandruff
3	=	Moderate dandruff
4	=	Marked dandruff (moderate to severe dandruff)
5	=	Severe dandruff

Loose dandruff was defined as flakes which have been separated from the scalp and become enmeshed in the hair. Adherent dandruff was defined as that which adhered to the scalp. Loose and adherent dandruff scores were summed to yield total dandruff scores.

Itching: Subjects independently evaluated itching of the scalp according to the following scale:

0	=	No itching
1	=	Mild itching
2	=	Moderate itching
3	=	Marked itching (moderate to severe itching)
4	=	Severe itching

f. Safety Evaluation: Patients were examined for adverse reactions during the course of the study.

Results: The reviewers have checked the line listings and agree with the sponsor's interpretation of the data. Therefore, the results given below are based on those of the sponsor.

a. Evaluable Patients: A total of 166 subjects were entered into the study. One subject did not receive any treatment and was excluded for both safety and efficacy analyses. The remainder of the patients were evaluable for safety. The number

of patients entered per treatment group was as follows:

Treatment	Number
Vehicle	41
0.3% ketoconazole	42
1% ketoconazole	41
2% ketoconazole	41

There were 6 subjects who prematurely discontinued the study, and the sponsor has disqualified them from the efficacy analyses. These were as follows:

Treatment	Reason for discontinuance (n)
Vehicle	Request of patient (1)
0.3% ketoconazole	Protocol violation (2)
1% ketoconazole	Request of patient (2)
1% ketoconazole	Lost to follow-up (1)

Therefore, the number of efficacy evaluable patients was as follows:

Treatment	Number
Vehicle	40
0.3% ketoconazole	40
1% ketoconazole	38
2% ketoconazole	41

There were also missed visits for some patients, but the patients were considered to be evaluable for efficacy.

b. Demographics: The demographics for the evaluable patients are displayed below:

	Treatment Group			
	Vehicle Control	Ketoconazole 0.3%	Ketoconazole 1.0%	Ketoconazole 2.0%
Evaluable Subjects	40 (100%)	40 (100%)	38 (100%)	41 (100%)
Sex				
Male	16 (40%)	14 (35%)	13 (34%)	15 (37%)
Female	24 (60%)	26 (65%)	25 (66%)	26 (63%)
Race				
Black	2 (5%)	3 (8%)	1 (3%)	1 (2%)
Caucasian	35 (88%)	37 (93%)	34 (89%)	39 (95%)
Other	3(8%)	0	3 (8%)	1 (2%)
Age (yrs)				
N	40 (100%)	40 (100%)	38 (100%)	41 (100%)
Mean	41.9	42.0	42.4	40.8
Min-Max	18-63	20-79	18-65	20-68

It is noted that there is a low percentage of minority subjects in this study.

The demographics for all patients who were treated are displayed below:

	Treatment			
	Vehicle Control	Ketoconazole 0.3%	Ketoconazole 1.0%	Ketoconazole 2.0%
All Treated Subjects	41(100%)	42(100%)	41(100%)	41(100%)
SEX				
Male	16(39%)	15(36%)	14(34%)	15(37%)
Female	25(61%)	27(64%)	27(66%)	26(63%)
Race				
Black	2(5%)	4(10%)	1(2%)	1(2%)
Caucasian	36(88%)	38(90%)	37(90%)	39(95%)
Other	3(7%)	0	3(7%)	1(2%)
Age (YRS.)				
N	41(100%)	42(100%)	41(100%)	41(100%)
Mean	41.8	41.9	41.3	40.8
MIN-MAX	18-63	20-79	18-65	20-68

c. Effectiveness: The results at the end of treatment (8 weeks) and at the 2 week follow-up (10 weeks) are given.

i. Adherent dandruff - the mean scores (of a maximum possible 5) and % reduction from baseline are given.

	Treatment Group			
Visit	Vehicle Control	0.3% ketoconazole	1% ketoconazole	2% ketoconazole
Baseline				
N	40	40	38	41
Mean Score	3.97	3.97	3.97	3.90
8 Weeks				
N	40	40	38	41
Mean Score %	2.80 (29%)	1.88 (53%)	1.34 (66%)	1.22 (69%)
10 Weeks				
N	39	39	38	40
Mean Score %	2.69 (32%)	1.56 (61%)	1.63 (59%)	1.25 (68%)

ii. Loose dandruff

	Treatment Group			
Visit	Vehicle Control	0.3% ketoconazole	1% ketoconazole	2% ketoconazole
Baseline				
N	40	40	38	41
Mean Score	3.77	3.72	3.74	3.80
8 Weeks				
N	40	40	38	41
Mean Score %	2.35 (38%)	1.50 (60%)	1.26 (66%)	1.10 (71%)
10 Weeks				
N	39	39	38	40
Mean Score %	2.08 (46%)	1.49 (60%)	1.42 (62%)	1.07 (72%)

iii. Total dandruff

Treatment Group				
Vehicle	Vehicle Control	0.3% ketoconazole	1% ketoconazole	2% ketoconazole
Baseline				
N	40	40	38	41
Mean Score	7.75	7.70	7.71	7.71
8 Weeks				
N	40	40	38	41
Mean Score %	5.15 (33%)	3.38 (56%)	2.61 (66%)	2.32 (70%)
10 Weeks				
N	39	39	38	40
Mean Score %	4.77 (39%)	3.05 (61%)	3.05 (60%)	2.32 (70%)

iv. Itching - the mean scores (of a maximum possible 4) and % reduction from baseline are given.

Treatment Group				
Vehicle	Vehicle Control	0.3% ketoconazole	1% ketoconazole	2% ketoconazole
Baseline				
N	40	40	38	41
Mean Score	1.57	1.70	1.59	1.51
8 Weeks				
N	40	40	38	41
Mean Score %	1.07 (32%)	0.63 (63%)	0.61 (61%)	0.39 (74%)
10 Weeks				
N	39	39	38	40
Mean Score %	1.18 (26%)	0.71 (56%)	0.87 (44%)	0.57 (61%)

d. Safety Evaluation: There were no reported adverse reactions in this study.

Comment: According to the sponsor's statistical analysis, all test groups (including vehicle) were statistically significant in dandruff and itching reduction at weeks 8 and 10 vs. baseline (all p-values 0.03 or less).

However, when pairwise comparisons between treatment groups were made, there were two comparisons which did not reflect statistical superiority (p = 0.05 or less) for active over vehicle. At weeks 8 and 10, the 1% ketoconazole product group was not significantly better in itching; although at week 8 it was nearly significant (p = 0.0625). The 0.3% ketoconazole product was also not better than vehicle in loose dandruff reduction at week 10 (p=0.08).

The results in general give the impression that the 2% ketoconazole product performs slightly better than the other active products, but the sponsor's analysis did not detect any statistically significant differences between the active groups. The 2% product was significantly better than vehicle for all parameters at weeks 8 and 10.

One may logically ask why the sponsor felt that this study justified the choice of 1% ketoconazole for OTC development, since it appears that the 0.3% product performs about as well and would (theoretically) present less risk to the user. The sponsor has provided a series of graphic representations of treatment differences by sex and scalp oiliness which unfortunately have no line listing backup or statistical analysis. The sponsor asserts that in females, only the 2% ketoconazole product was better than vehicle, but that effectiveness increased with increased amounts of ketoconazole. The sponsor feels that this may have been caused by generally longer hair in female groups.

In summary, this dose-ranging study is unconvincing as support for choosing 1% ketoconazole over the other strengths. However, if the pivotal efficacy studies and safety evaluation establish the 1% ketoconazole product to be safe and effective, this study is not a reason to disapprove the application.

2. Study Title: An evaluation of the Safety in Long-Term Use and Efficacy of an Anti-Dandruff Shampoo. (J&J Protocol No. 16399.41 A)

Investigator: J. Kantor, M.D.
Research Testing Laboratories, Inc.
Great Neck, N.Y. 11021

Method:

a. Study Design: This was a single-center, open-label study of the safety and effectiveness of ketoconazole shampoo, 1%.

b. Patient Selection: All patients were recruited from the dose-ranging study described above. All patients were 18 years of age and older and underwent at least a 2 week washout period

from the end of the dose-ranging study to the beginning of this one. The patients were required to have a scalp erythema/irritation score of 0 or ± (minimal erythema) on each of 7 defined areas of the scalp on study entrance, or a total erythema/irritation score of less than 2 or a scale from 0 = no irritation to 4 = severe erythema/excoriations. These two entrance criteria do not appear to be equivalent; that is, a patient who met the second criteria (total score less than 2) may have had considerably more erythema/irritation than someone who met the first. However, review of the line listings indicates that only one patient (of 102) entered the study with an erythema/irritation score of 2. All other patients entered with scores of 0 or ±.

c. Patient Exclusions: The patient exclusions were the same as for study A.1. above.

d. Dosage and duration of treatment: The patients were told to use Prell Shampoo for one week prior to the start of the study. They were then told to shampoo 4 to 10 times weekly with 1% ketoconazole shampoo for 12 months. In the event that a subject experienced appreciable erythema or irritation of the scalp, the frequency of use could be decreased. The subjects were instructed to use about 15 mL of shampoo, lather, rinse and repeat.

e. Effectiveness parameters: The patients returned for evaluation at 1, 2, 4, 6, 8, 10, and 12 months. The same effectiveness parameters were evaluated as for study A.1. above.

f. Safety Evaluation: At each evaluation, the investigator examined seven scalp segments (top front, top back, left side, right side, middle left, middle right, bottom back) for erythema and irritation, using the following grading scale:

0	No evidence of irritation
±	Minimal presence of erythema
1	Slight definite erythema
2	Moderate erythema/some skin flaking
3	Marked erythema/skin flaking/some papules
4	Severe erythema/excoriations.

The patients were also examined for other types of adverse reactions. The protocol provided an option for a patch test of any patient who had an adverse skin reaction of any type.

Finally, 48 volunteers were tested during the ninth month of therapy for plasma ketoconazole levels.

Results:

a. Evaluable Patients: A total of 102 subjects were entered into the study. Seven of these discontinued the study prematurely. The reasons for discontinuance were: adverse event (1), unrelated intercurrent illness (1), lost to follow-up (1), and subject request (apparently unrelated to therapy, although this is not stated) (4).

b. Demographics: The demographics for all patients who entered the study are displayed below:

All Treated Subjects	102 (100%)
SEX	
Male	34 (33%)
Female	68 (67%)
RACE	
Black	4 (4%)
Caucasian	94 (92%)
Hispanic	3 (3%)
Other	1 (<1%)
AGE (YRS)	
N	102 (100%)
Mean	42.3
Min-Max	21-79

c. Effectiveness: The results at the end of 12 months of therapy are given.

i. Dandruff - the mean scores (of a possible 5) and % reduction for loose and adherent dandruff are given, as well as the mean scores (of a possible 10) and % reduction for total dandruff.

Visit	Adherent	Loose	Total
Baseline			
N	102	102	102
Mean Score	2.3	2.1	4.4
12 Months			
N	95	95	95
Mean Score %	0.9 (61%)	0.6 (71%)	1.5 (66%)

ii. Itching - the mean scores (of a maximum possible 4) and % reduction from baseline are given.

Visit	Itching
Baseline	
N	102
Mean Score	1.2
12 Months	
N	95
Mean Score %	0.4 (67%)

d. Safety Evaluation:

i. Erythema/irritation - Eight of 102 subjects (8%) experienced occasional erythema/irritation during the study. Six of these reported these symptoms only during the first month of therapy. All episodes spontaneously resolved before the end of treatment. The highest score seen at any time was a 2 (of a possible 4).

ii. Other adverse experience. There were 5 other reactions which were probably or possibly related to therapy. One of these (tenderness of the scalp) caused the patient to discontinue the study. The other reactions were ear pain (2), seborrhea and urticaria.

iii. Ketoconazole levels. No ketoconazole levels were detected in any of the patients tested (detection level 5 ng/mL). These results are difficult to interpret because there is no record of whether the volunteers used the shampoo frequently. The sponsor reports that 38/102 subjects reported using the shampoo less than the specified 4 times per week. Overall, the mean usage was 4.4 shampoo per week over the 12 month test period.

Comment: This 12-month study is useful in establishing that there is a relatively low incidence of adverse events over a relatively long treatment period in a closely monitored group of patients. Reactions of all types totaled 13 (13%), most of which were mild erythema/irritation reactions which resolved spontaneously.

The analysis of a random group of patients for systemic ketoconazole levels is interesting, but was not done precisely enough to provide meaningful safety data.

3. Study Title: A Multi-Center Evaluation of 1% Ketoconazole Shampoo and Placebo Shampoo in Treatment of Dandruff (J&J Protocol No. 16399.41B)

Investigators:

Irwin Kantor, M.D.
Research Testing Laboratories, Inc.
Great Neck, N.Y.

Colleen McClellan Parker, M.D.
Walker Clinical Evaluations, Inc.
Indianapolis, Indiana

Debra L. Breneman, M.D.
University of Dermatology, Consultants, Inc.
Cincinnati, Ohio

Everett L. Jones, M.D.
Hill Top Research, Inc.
Miamiville, Ohio

Frank E. Dunlap, M.D.
Argus Research, Inc.
Tucson, Arizona

Janet G. Hickman, M.D.
The Education & Research Foundation, Inc.
Lynchburg, Virginia

Method:

a. Study Design: This was a randomized, multicenter, double-blind, parallel group comparison of the effectiveness and safety of 1% ketoconazole shampoo and its vehicle.

b. Patient Selection: Patients of either sex, 18 years of age and older were entered into the study. The patients were required to have a total adherent dandruff score of 14 at study entrance as determined by dividing the scalp into 6 segments and scoring each section on a scale from 0 = no scaling to 9-10 =

extremely severe scaling. The patients were not to use any other anti-dandruff medications during the course of the study.

c. Patient Exclusions: The patient exclusions were the same as in Study A.1., above, with two additions:

- a scalp irritation score of 2 or more for the entire scalp on a scale from 0 = no irritation to 4 = intense irritation.
- if female and of child-bearing potential and not using a recognized method of contraception.

d. Dosage and duration of treatment: Patients were instructed to shampoo with Prell (non-medicated) Shampoo exclusively for 2 weeks prior to treatment initiation. Subjects were then randomized to one of the treatment groups using stratification for sex, baseline adherent dandruff rating, and baseline scalp oiliness. They were instructed to shampoo twice weekly at home for 8 weeks. The study days designated for shampooing were 3, 7, 10, 14, 17, 21, 24, 28, 31, 35, 38, 42, 45, 49, and 52. The subjects were instructed to use their regular shampoo during the 2 week follow-up period. They were instructed to use "sufficient shampoo to produce a generous lather".

e. Effectiveness parameters: The patients returned for evaluation at weeks 2, 4, 6, and 8. They were contacted by telephone at 2 weeks after the end of the study to determine whether any adverse reactions had occurred. The following parameters were evaluated:

Dandruff: The investigator (dermatologist) combed the subject's hair to divide the scalp into six segments and scored each segment individually for adherent and loose types to dandruff according to the following scale:

0	=	No Scaling
1-2	=	Mild Scaling
3-4	=	Moderate Scaling
5-6	=	Marked Scaling
7-8	=	Severe Scaling
9-10	=	Extremely Severe, Heavy Scaling

The six scalp segments evaluated included top left scalp, left side scalp, left back scalp, top right scalp, right side scalp, and right back scalp.

The adherent and loose dandruff scores for each of the six scalp segments were summed to yield total adherent dandruff and total loose dandruff scores, respectively. The total adherent dandruff and total loose dandruff scores were then summed to yield total dandruff scores.

Itching: Subjects evaluated itching of the scalp according to the following scale:

0	=	No Itching
1	=	Mild Itching
2	=	Moderate Itching
3	=	Marked Itching (moderate to severe itching)
4	=	Severe Itching

Global Assessments of Efficacy: At the end of treatment the investigator evaluated the subject's dandruff using the following scale:

1	=	Completely cleared
2	=	Marked improvement
3	=	Moderate improvement
4	=	Slight improvement
5	=	No improvement or worsening

f. Safety Evaluation: Patients were examined for adverse reactions during the course of the study. In addition, the investigator scored any irritation on the entire scalp using the following scale:

0	=	No evidence of irritation
1	=	Minimal irritation
2	=	Moderate irritation
3	=	Marked irritation
4	=	Intense irritation

Results: The reviewers have checked the line listings and agree with the sponsor's interpretation of the data. It should be noted that there was prior agreement between the sponsor and FDA that this study could be split into two separate studies for the purposes of analyses. One group includes Drs. Kantor, Breneman and Dunlap, while the other includes Drs. Parker, Jones and Hickman. For the purpose of convenience, the results of the two groups will be presented consecutively below. However, they do constitute two separate and distinct studies.

a. Evaluable patients: There were a total of 795 subjects entered into the study at 6 centers. A total of 478 was randomized to ketoconazole and 317 to vehicle (this imbalance was

intended in the study protocol). The following table presents the number of subjects at each center and by group who were entered, treated, discontinued, and found to be non-evaluable.

Number of Subjects - Group 1				
Investigator	Randomized	Treated	Discontinued	Non-evaluable
Kantor	109	104	13	11
Breneman	150	150	7	5
Dunlap	123	122	4	1
Total	382	376	24	17

Number of Subjects - Group 2				
Investigator	Randomized	Treated	Discontinued	Non-Evaluable
Parker	159	153	19	12
Jones	125	124	5	5
Hickman	129	127	12	11
Total	413	404	36	28

Number of Subjects			
	Vehicle	Ketoconazole	Total
Group 1	152	230	382
Group 2	165	248	413
Total	317	478	795

All patients who were treated at any time were evaluable for safety (n=780).

The following tables represents the number of patients who (a) discontinued early and (b) were not evaluable for efficacy for both groups.

Vehicle n (%) - Total = 317		
Reason for discontinuation	Evaluable	Not Evaluable
Protocol Violation	4 (1%)	6 (2%)
Subject Request	0	3 (<1%)
Unrelated intercurrent illness	2 (<1%)	2 (<1%)
Adverse reaction	1 (<1%)	0
Other*	0	3 (<1%)
Total Discontinued	7 (2%)	14 (4%)
Total Completed Study	295 (93%)	1 (<1%)
Total Subjects	302 (95%)	15 (5%)

Ketoconazole n (%) - Total = 478		
Reason for Discontinuation	Evaluable	Not Evaluable
Protocol violation	2 (<1%)	8 (2%)
Subject request	3 (<1%)	7 (1%)
Unrelated intercurrent illness	2 (<1%)	0
Adverse reaction	0	1 (<1%)
Other*	2 (<1%)	14 (3%)
Total Discontinued	9 (2%)	30 (6%)
Total Completed Study	439 (92%)	0
Total Subjects	448 (94%)	30 (6%)

*Other included: patient was never treated (failure to return after baseline visit), 10; missed visits, 5; lost to follow-up, 2; pregnancy, 1; and death unrelated to therapy, 1.

b. Demographics: The demographics for all patients entering the studies were as follows:

	Group 1		Group 2	
	Vehicle Placebo	Ketoconazole 1%	Vehicle Placebo	Ketoconazole 1%
All Randomized Subjects	152 (100%)	230 (100%)	165 (100%)	248 (100%)
SEX				
Male	85 (56%)	126 (55%)	76 (46%)	114 (46%)
Female	67 (44%)	104 (45%)	89 (54%)	134 (54%)
RACE				
Asian	4 (3%)	3 (1%)	0	0
Black	27 (18%)	39 (17%)	12 (7%)	8 (3%)
Caucasian	115 (76%)	177 (77%)	151 (92%)	240 (97%)
Hispanic	3 (2%)	4 (2%)	0	0
Oriental	1 (<1%)	2 (<1%)	0	0
Other	2 (1%)	5 (2%)	2 (1%)	0
AGE (yrs.)				
N	152 (100%)	230 (100%)	165 (100%)	248 (100%)
Mean	42.1	42.0	44.2	43.6
Min-Max	18-79	18-77	18-74	18-78

c. Effectiveness: The results are presented at the end of treatment (8 weeks).

i. Adherent Dandruff - the maximum possible score is 60 (6 scalp areas x score of 10). The % figure in the 8 week "Mean" column represents decrease from baseline. The % figure in the "N" column represents percentage of evaluable patients.

	Group 1		Group 2	
Visit	Vehicle	Ketoconazole	Vehicle	Ketoconazole
Baseline				
N	148 (100%)	217 (100%)	154 (100%)	231 (100%)
Mean	24.4	24.2	24.1	23.6
8 Weeks				
N	143 (97%)	209 (96%)	149 (97%)	226 (98%)
Mean	17.3 (29%)	6.1 (75%)	22.0 (10%)	10.7 (55%)
p-value	0.0001		0.0001	

ii. Loose dandruff - the maximum possible score is 60.

	Group 1		Group 2	
Visit	Vehicle	Ketoconazole	Vehicle	Ketoconazole
Baseline				
N	148 (100%)	217 (100%)	154 (100%)	231 (100%)
Mean	14.8	14.4	13.4	13.4
8 Weeks				
N	143 (97%)	209 (96%)	149 (97%)	226 (98%)
Mean	10.0 (32%)	4.2 (71%)	10.7 (20%)	4.9 (63%)
p-value	0.0001		0.0001	

iii. Total dandruff - the maximum possible score is 120.

	Group 1		Group 2	
Visit	Vehicle	Ketoconazole	Vehicle	Ketoconazole
Baseline				
N	148 (100%)	217 (100%)	154 (100%)	231 (100%)
Mean	39.2	38.6	37.5	37.0
8 Weeks				
N	143 (97%)	209 (96%)	149 (97%)	226 (98%)
Mean	27.3 (30%)	10.3 (73%)	32.7 (13%)	15.6 (58%)
p-value	0.0001		0.0001	

iv. Itching - the maximum possible score is 4.

	Group 1		Group 2	
Visit	Vehicle	Ketoconazole	Vehicle	Ketoconazole
Baseline				
N	148 (100%)	217 (100%)	153 (100%)	230 (100%)
Mean	2.0	2.0	1.7	1.7
8 Weeks				
N	143 (97%)	208 (96%)	148 (97%)	227 (97%)
Mean	1.3 (35%)	0.8 (60%)	1.4 (18%)	0.9 (47%)
p-value	0.0001		0.0001	

v. Global assessment of efficacy at end of treatment by investigator

	Group 1		Group 2	
	Vehicle	Ketoconazole 1%	Vehicle	Ketoconazole 1%
Evaluable Subjects	148 (100%)	217 (100%)	154 (100%)	231 (100%)
Investigator Evaluation				
Completely cleared	8 (5%)	94 (43%)	2 (1%)	40 (17%)
Marked Improvement	17 (11%)	43 (20%)	4 (3%)	79 (34%)
Moderate Improvement	32 (22%)	18 (8%)	35 (23%)	53 (23%)
Slight Improvement	38 (26%)	18 (8%)	48 (31%)	31 (13%)
No Improvement or Worsening	51 (34%)	13 (6%)	61 (40%)	24 (10%)

d. Safety Evaluation:

i. Adverse reactions. Eight subjects were discontinued from the study because of adverse events and/or intercurrent illnesses. Only two of these were probably or possibly related to therapy: one vehicle patient discontinued due to contact dermatitis, and one active shampoo patient discontinued because of headache caused by the smell of the product.

In all, there were 12 adverse events in the ketoconazole group which were probably or possibly related to treatment (12/465 = 3%). There were 9 adverse events in the vehicle group which were probably or possibly related (9/315 = 3%). The following table categorizes the reactions by investigator:

Investigator	Reaction Type	Vehicle	Ketoconazole
Kantor	0	0	0
Breneman	Contact Dermatitis	1	0
	Eczema	1	0
Dunlap	Application site rx.	1	0
	Acne	1	0
	Rash	0	1
Parker	Pruritus	1	2
	Rash	1	2
	Application site rx.	0	1
	Urticaria	0	1
Jones	Rash	1	0
Hickman	Urticaria	1	0
	Conjunctivitis	1	1
	Pruritus	0	1
	Eye pain	0	1
	Acne	0	1
	Headache	0	1
TOTAL		9	12

It is apparent that Drs. Parker and Hickman (Group 2) contributed most of the reports. The percentage of adverse events for the Group 2 ketoconazole patients is 11/201 = 5%.

ii. Irritation: The data is presented in terms of patients who experienced increased or decreased irritation. Data is presented at week 8.

	Group 1		Group 2	
Irritation Status	Vehicle	Ketoconazole	Vehicle	Ketoconazole
Increased	2 (1%)	2 (<1%)	20 (12%)	8 (3%)
No change	139 (91%)	197 (88%)	114 (70%)	181 (75%)
Decreased	5 (3%)	12 (5%)	17 (10%)	40 (17%)
Missing	0	3 (1%)	2 (1%)	2 (<1%)

iii. All adverse reactions: The following tables, which were taken directly from the sponsor's submission, present all adverse reactions, whether related to therapy or not.

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Table 10.1: Summary of Adverse Events by Treatment Group and Severity For All Treated Subjects - All Medical Problems

Body System COSTART Term	Vehicle Placebo Mild	Mod	Sev	Unk	Total	Ketoconazole 1% Mild	Mod	Sev	Unk	Total
Number of Subjects					315(100%)					465(100%)
Subjects Reporting Adverse Events	61	36	15	0	112(36%)	89	45	17	0	151(32%)
Coded Term*										
Body as a Whole	24	4	7	0	35(11%)	32	9	2	0	43(9%)
FEVER	0	0	0	0	0(0%)	1	0	0	0	1(<1%)
FLU SYND	3	1	2	0	6(2%)	8	5	0	0	13(3%)
HEADACHE	17	2	5	0	24(8%)	23	4	2	0	29(6%)
INFECT	2	1	0	0	3(<1%)	0	0	0	0	0(0%)
INJURY ACCID	1	0	0	0	1(<1%)	0	0	0	0	0(0%)
PAIN	0	0	0	0	0(0%)	3	0	0	0	3(<1%)
PHYSICAL EXAMINATION	1	0	0	0	1(<1%)	0	0	0	0	0(0%)
REACT UNEVAL	1	0	0	0	1(<1%)	0	0	0	0	0(0%)
Cardiovascular	3	1	0	0	4(1%)	1	1	3	0	5(1%)
EXTRASYSTOLES VENT	0	0	0	0	0(0%)	0	1	0	0	1(<1%)
HYPERTENS	0	1	0	0	1(<1%)	0	1	0	0	1(<1%)
MIGRAINE	1	0	0	0	1(<1%)	0	0	1	0	1(<1%)
PAIN CHEST	0	0	0	0	0(0%)	0	0	1	0	1(<1%)
SUDDEN DEATH	0	0	0	0	0(0%)	0	0	1	0	1(<1%)
TACHYCARDIA	1	0	0	0	1(<1%)	1	0	0	0	1(<1%)
VASC DIS PERIPH	1	0	0	0	1(<1%)	0	0	0	0	0(0%)

Percents are based on the number of treated subjects in each treatment group.
* When a subject had multiple incidences of a given event only the most severe is summarized.

26(a)

Appendix A

Table 10.1: Summary of Adverse Events by Treatment Group and Severity For All Treated Subjects - All Medical Problems

Body System COSTART Term	Vehicle Placebo					Ketoconazole 1%				
	Mild	Mod	Sev	Unk	Total	Mild	Mod	Sev	Unk	Total
Coded Term*										
Digestive	12	5	0	0	17(5%)	7	8	1	0	16(3%)
COLITIS	1	0	0	0	1(<1%)	0	0	0	0	0(0%)
CONSTIP	1	0	0	0	1(<1%)	0	0	0	0	0(0%)
DIARRHEA	1	2	0	0	3(<1%)	3	0	0	0	3(<1%)
DYSPEPSIA	2	1	0	0	3(<1%)	1	0	0	0	1(<1%)
DYSPHAGIA	0	0	0	0	0(0%)	0	1	0	0	1(<1%)
FLATUL	1	0	0	0	1(<1%)	0	0	0	0	0(0%)
GASTRITIS	0	0	0	0	0(0%)	0	1	0	0	1(<1%)
GINGIVITIS	1	0	0	0	1(<1%)	0	0	0	0	0(0%)
INFECT	0	0	0	0	0(0%)	0	1	0	0	1(<1%)
JAUNDICE CHOLESTAT	0	0	0	0	0(0%)	0	1	0	0	1(<1%)
PAIN	1	1	0	0	2(<1%)	0	1	0	0	1(<1%)
PAIN ABDO	1	0	0	0	1(<1%)	0	0	0	0	0(0%)
RECTAL DIS	1	0	0	0	1(<1%)	0	0	0	0	0(0%)
SURGERY	0	1	0	0	1(<1%)	0	0	0	0	0(0%)
TOOTH CARIES	1	0	0	0	1(<1%)	1	1	0	0	2(<1%)
TOOTH DIS	2	0	0	0	2(<1%)	3	2	1	0	6(1%)
Metabolic and Nutritional	0	0	1	0	1(<1%)	1	1	1	0	3(<1%)
GOUT	0	0	0	0	0(0%)	0	1	1	0	2(<1%)
HYPERCHOLESTEREM	0	0	0	0	0(0%)	1	0	0	0	1(<1%)
HYPOGLYCEM	0	0	1	0	1(<1%)	0	0	0	0	0(0%)

Percents are based on the number of treated subjects in each treatment group.
* When a subject had multiple incidences of a given event only the most severe is summarized.

Appendix A

Table 10.1: Summary of Adverse Events by Treatment Group and Severity For All Treated Subjects - All Medical Problems

Body System COSTART Term	Vehicle Placebo Mild	Mod	Sev	Unk	Total	Ketoconazole 1% Mild	Mod	Sev	Unk	Total
Coded Term*										
Musculoskeletal	4	4	6	0	14(4%)	11	8	1	0	20(4%)
ARTHRALGIA	1	0	0	0	1(<1%)	1	0	0	0	1(<1%)
ARTHRITIS	0	1	0	0	1(<1%)	2	1	0	0	3(<1%)
BONE FRACT SPONTAN	0	1	0	0	1(<1%)	0	1	0	0	1(<1%)
BURSITIS	1	0	0	0	1(<1%)	0	0	0	0	0(0%)
INJURY ACCID	0	1	3	0	4(1%)	0	2	0	0	2(<1%)
JOINT DIS	0	0	1	0	1(<1%)	0	1	0	0	1(<1%)
MYALGIA	0	1	0	0	1(<1%)	2	0	0	0	2(<1%)
NECK RIGID	0	0	0	0	0(0%)	1	0	0	0	1(<1%)
ORTHOPEDIC SURGERY	0	0	1	0	1(<1%)	0	0	0	0	0(0%)
PAIN	1	0	1	0	2(<1%)	0	1	0	0	1(<1%)
PAIN BACK	2	0	2	0	4(1%)	3	2	0	0	5(1%)
PAIN NECK	0	0	0	0	0(0%)	1	0	0	0	1(<1%)
TENDON DIS	0	0	0	0	0(0%)	1	0	1	0	2(<1%)
Nervous System	2	2	0	0	4(1%)	1	0	0	0	1(<1%)
DEPRESSION	1	1	0	0	2(<1%)	0	0	0	0	0(0%)
DIZZINESS	1	0	0	0	1(<1%)	0	0	0	0	0(0%)
NERVOUSNESS	0	0	0	0	0(0%)	1	0	0	0	1(<1%)
SCLEROSIS MULT	0	1	0	0	1(<1%)	0	0	0	0	0(0%)

Percents are based on the number of treated subjects in each treatment group.
* When a subject had multiple incidences of a given event only the most severe is summarized.

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Appendix A

Table 10.1: Summary of Adverse Events by Treatment Group and Severity For All Treated Subjects - All Medical Problems

Body System COSTART Term	Vehicle Placebo					Ketoconazole 1%				
	Mild	Mod	Sev	Unk	Total	Mild	Mod	Sev	Unk	Total
Coded Term*										
Respiratory	38	15	1	0	54(17%)	43	17	8	0	68(15%)
BRONCHITIS	0	1	0	0	1(<1%)	1	3	1	0	5(1%)
COUGH INC	2	0	0	0	2(<1%)	1	0	0	0	1(<1%)
INFECT	27	9	1	0	37(12%)	37	5	1	0	43(9%)
LARYNGITIS	0	1	0	0	1(<1%)	0	0	0	0	0(0%)
PHARYNGITIS	0	2	0	0	2(<1%)	1	1	2	0	4(<1%)
PNEUMONIA	0	0	0	0	0(0%)	0	1	1	0	2(<1%)
PNEUMOTHORAX	0	0	0	0	0(0%)	0	0	1	0	1(<1%)
RHINITIS	2	0	0	0	2(<1%)	2	0	0	0	2(<1%)
SINUSITIS	12	3	0	0	15(5%)	7	8	3	0	18(4%)
Skin	10	3	0	0	13(4%)	12	2	1	0	15(3%)
ACNE	1	0	0	0	1(<1%)	1	0	0	0	1(<1%)
ALOPECIA	1	0	0	0	1(<1%)	0	0	0	0	0(0%)
APPLICAT SITE REACT	2	0	0	0	2(<1%)	1	0	0	0	1(<1%)
CYST	1	0	0	0	1(<1%)	2	1	0	0	3(<1%)
DERM CONTACT	0	1	0	0	1(<1%)	0	0	0	0	0(0%)
ECZEMA	1	0	0	0	1(<1%)	0	0	0	0	0(0%)
HERPES SIMPLEX	1	0	0	0	1(<1%)	1	0	0	0	1(<1%)
HERPES ZOSTER	0	1	0	0	1(<1%)	0	0	0	0	0(0%)
INFECT	0	0	0	0	0(0%)	1	0	0	0	1(<1%)
PRURITUS	1	0	0	0	1(<1%)	3	0	0	0	3(<1%)
RASH	1	1	0	0	2(<1%)	4	0	0	0	4(<1%)
SWEAT	1	0	0	0	1(<1%)	0	0	0	0	0(0%)

Percents are based on the number of treated subjects in each treatment group.
* When a subject had multiple incidences of a given event only the most severe is summarized.

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Appendix A

Table 10.1: Summary of Adverse Events by Treatment Group and Severity For All Treated Subjects - All Medical Problems

Body System COSTART Term	Vehicle Placebo					Ketoconazole 1%				
	Mild	Mod	Sev	Unk	Total	Mild	Mod	Sev	Unk	Total
Coded Term*										
Skin										
TRAUMA	0	0	0	0	0(0%)	0	1	0	0	1(<1%)
URTICARIA	0	1	0	0	1(<1%)	0	0	1	0	1(<1%)
Special Senses	4	2	0	0	6(2%)	3	3	0	0	6(1%)
BLEPHARITIS	1	0	0	0	1(<1%)	0	0	0	0	0(0%)
CONJUNCTIVITIS	1	0	0	0	1(<1%)	1	0	0	0	1(<1%)
EAR DIS	1	0	0	0	1(<1%)	0	0	0	0	0(0%)
HEADACHE	0	0	0	0	0(0%)	0	1	0	0	1(<1%)
OTITIS MED	0	1	0	0	1(<1%)	1	0	0	0	1(<1%)
PAIN EAR	1	1	0	0	2(<1%)	1	1	0	0	2(<1%)
PAIN EYE	0	0	0	0	0(0%)	0	1	0	0	1(<1%)
Urogenital	7	6	2	0	15(5%)	5	4	1	0	10(2%)
CYSTITIS	1	0	0	0	1(<1%)	0	0	0	0	0(0%)
DYSMENORRHEA	4	0	1	0	5(2%)	3	1	1	0	5(1%)
ELECTIVE SURGERY	0	0	0	0	0(0%)	1	0	0	0	1(<1%)
HEM VAGINAL	0	0	0	0	0(0%)	0	1	0	0	1(<1%)
HEMATURIA	1	0	0	0	1(<1%)	0	0	0	0	0(0%)
INFECT URIN TRACT	1	1	0	0	2(<1%)	0	1	0	0	1(<1%)
KIDNEY FUNC ABNORM	0	3	0	0	3(<1%)	0	0	0	0	0(0%)
MENS DIS	0	0	0	0	0(0%)	0	1	0	0	1(<1%)
METRORRHAGIA	0	1	0	0	1(<1%)	0	0	0	0	0(0%)
PREGN DIS	0	0	1	0	1(<1%)	0	0	0	0	0(0%)

Percents are based on the number of treated subjects in each treatment group.
* When a subject had multiple incidences of a given event only the most severe is summarized.

26(e)

Appendix A

Table 10.1: Summary of Adverse Events by Treatment Group and Severity For All Treated Subjects - All Medical Problems

Body System COSTART Term	Vehicle Placebo					Ketoconazole 1%				
	Mild	Mod	Sev	Unk	Total	Mild	Mod	Sev	Unk	Total
Coded Term*										
Urogenital										
PROSTAT DIS	0	1	0	0	1(<1%)	0	0	0	0	0(0%)
VAGINITIS	0	0	0	0	0(0%)	1	0	0	0	1(<1%)

Percents are based on the number of treated subjects in each treatment group.
* When a subject had multiple incidences of a given event only the most severe is summarized.

Comment: These studies establish that ketoconazole shampoo, 1% is superior to its vehicle in the treatment of dandruff and related itching under the test conditions. While the two investigator groups found absolute differences in reduction of dandruff (73% for Group 1 vs. 58% for Group 2), the margin of superiority of active over vehicle was consistent (43% for Group 1 and 45% for Group 2).

Similarly, for itching the Group 1 investigators found a 25% difference in reduction of itching between active and vehicle while Group 2 investigators found a 29% difference. Because the number of patients studied was relatively large, all these differences were highly statistically significant (p=0.0001).

The global evaluation was more strongly in favor of active over vehicle in Group 1 than in Group 2, although the active product was greatly superior in both groups.

The number and types of adverse reactions were well within the limits expected in studies of this type. There were 12 reactions in the active group (3% of safety evaluable patients), and none of these were associated with systemic toxicity.

Since the dose-ranging study suggested that the product is more effective in males than females, the sponsor was asked to submit an efficacy analysis by gender. The following tables, taken directly from the sponsor's submission, reflect the data:

NDA: 20-310

MEDIC Ketoconazole 1% Shampoo 19399-41B - Effect of Gender and Geography (analyzed 05NOV93)

SUM OF LOOSE DANDRUFF RATINGS @ 6 SITES

	GEOGRAPHIC GROUP (1 OR 2) SUBANALYSIS							
	1				2			
	Test Shampoo (0.0 Keto or 1.0 Keto)				Test Shampoo (0.0 Keto or 1.0 Keto)			
	0.0 Keto		1.0 Keto		0.0 Keto		1.0 Keto	
	Sex of Subject		Sex of Subject		Sex of Subject		Sex of Subject	
	F	M	F	M	F	M	F	M
	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean
Week of Study								
0	15.3	14.5	14.0	14.8	12.8	14.7	13.2	13.5
8	10.4	9.5	5.4	3.3	9.7	12.0	5.4	4.6

ADHERENT DANDRUFF (SUM OF 6 SITES)

	GEOGRAPHIC GROUP (1 OR 2) SUBANALYSIS							
	1				2			
	Test Shampoo (0.0 Keto or 1.0 Keto)				Test Shampoo (0.0 Keto or 1.0 Keto)			
	0.0 Keto		1.0 Keto		0.0 Keto		1.0 Keto	
	Sex of Subject		Sex of Subject		Sex of Subject		Sex of Subject	
	F	M	F	M	F	M	F	M
	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean
Week of Study								
0	24.1	24.7	24.0	24.6	22.6	26.1	22.2	25.3
8	17.1	17.7	8.2	4.3	20.6	23.5	10.6	10.8

NDA: 20-310

MEDIC Ketoconazole 1% Shampoo 19399-41B - Effect of Gender and Geography (analyzed 05NOV93)

OVERALL SUM OF LOOSE + ADHERENT DANDRUFF

	GEOGRAPHIC GROUP (1 OR 2) SUBANALYSIS							
	1				2			
	Test Shampoo (0.0 Keto or 1.0 Keto)				Test Shampoo (0.0 Keto or 1.0 Keto)			
	0.0 Keto		1.0 Keto		0.0 Keto		1.0 Keto	
	Sex of Subject		Sex of Subject		Sex of Subject		Sex of Subject	
	F	M	F	M	F	M	F	M
	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean
Week of Study								
0	39.4	39.2	37.9	39.4	35.4	40.8	35.4	38.8
8	27.5	27.2	13.6	7.6	30.3	35.5	16.0	15.4

ITCH RATINGS

	GEOGRAPHIC GROUP (1 OR 2) SUBANALYSIS							
	1				2			
	Test Shampoo (0.0 Keto or 1.0 Keto)				Test Shampoo (0.0 Keto or 1.0 Keto)			
	0.0 Keto		1.0 Keto		0.0 Keto		1.0 Keto	
	Sex of Subject		Sex of Subject		Sex of Subject		Sex of Subject	
	F	M	F	M	F	M	F	M
	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean
Week of Study								
0	1.9	2.0	2.1	1.9	1.8	1.7	1.9	1.5
8	1.3	1.3	0.9	0.7	1.4	1.4	1.0	0.8

NDA: 20-310

MEDIC Ketoconazole 1% Shampoo 19399-41B - Effect of Gender and Geography (analyzed 05NOV93)

	Test Shampoo (0.0 keto or 1.0 keto)			
	0.0 keto		1.0 keto	
	Sex of Subject		Sex of Subject	
	F	M	F	M
	N	N	N	N
Investigators Global Rating				
1-Cleared	7	3	51	83
2-Marked Improvement	7	14	56	66
3-Moderate Improvement	34	33	54	43
4-Slight Improvement	48	39	31	18
5-No Improvement	51	60	23	14
	147	149	215	224

	Geographic Group (1 or 2) Subanalysis							
	1				2			
	Test Shampoo (0.0 keto 1.0 keto)				Test Shampoo (0.0 keto 1.0 keto)			
	0.0 keto		1.0 keto		0.0 keto		1.0 keto	
	F	M	F	M	F	M	F	M
	N	N	N	N	N	N	N	N
Investigators Global Rating								
1-Cleared	5	3	29	65	2	.	22	18
2-Marked Improvement	4	13	20	23	3	1	36	43
3-Moderate Improvement	16	16	25	19	18	17	29	24
4-Slight Improvement	16	22	12	6	32	17	19	12
5-No Improvement	24	27	8	5	27	33	15	9

It can be seen that there is some evidence that males responded better than females in Group 1 in terms of total dandruff and global evaluation. However, the females also responded well, and there are no apparent differences between the sexes in Group 2. It may be stated that the product is effective in both sexes although it is probably more effective in males and females with short hair than in females with long hair.

4. Study Title: A Bioassay Study to Assess the Product Performance Equivalence of Two Anti-Dandruff Shampoo Formulations (J&J Protocol No. 163399.41C)

Investigator: Irwin Kantor, M.D.
Research Testing Laboratories, Inc.
Great Neck, N.Y.

Method:

a. Study design: This was a single-center, randomized, double-blind, parallel group comparison of ketoconazole 1% shampoo manufactured by two different methods. The pivotal studies described above were performed with drug made by a two-tank manufacturing process without de-aeration. The sponsor decided to switch to a single tank process with de-aeration to improve content uniformity of the shampoo. The product and manufacturing process are otherwise unchanged.

b. Patient Selection: Patients were selected from those who had participated in the long-term use study (protocol 16399.41A, above). All patients were 18 years of age or older, and were otherwise selected by the same criteria as are outlined in the summary of the long-term use study (see A.2. above).

c. Patient Exclusions: The exclusions were the same as for study A.1. above, except that a two-week washout period with a non-medicated shampoo was not necessary.

d. Dosage and duration of treatment: The subjects were told to shampoo 4 to 10 times weekly with the test medication dispensed to them for four weeks. the subjects were instructed to use about 15 mL of shampoo, lather, rinse and repeat.

e. Effectiveness parameters: The patients returned for evaluation at 4 weeks. The same effectiveness parameters were evaluated as for study A.1. above.

f. Safety evaluation: The same safety evaluations as were made for study A.2. above were made in this study, except that plasma ketoconazole levels were not tested.

Results:

a. Evaluable Patients: Fifty-two of the 102 patients who entered the long-term study continued into this study. None discontinued the study prematurely.

b. Demographics: Patient demographics are as follows. The "old" shampoo is manufactured by the two-tank process and was used in the pivotal clinical studies. The "new" shampoo was made by the one-tank process.

	"Old" Shampoo	"New" Shampoo
All Treated Subjects	16 (100%)	36 (100%)
SEX		
Male	6 (38%)	12 (33%)
Female	10 (63%)	24 (67%)
RACE		
Black	1 (6%)	2 (6%)
Caucasian	13 (81%)	32 (89%)
Hispanic	1 (6%)	2 (6%)
Oriental	1 (6%)	0
AGE (yrs.)		
N	16 (100%)	35 (100%)
Mean	43.7	46.3
Min-Max	26-67	26-69

c. Effectiveness: The results at the end of treatment (4 weeks) are given. The groups were not equivalent in size by protocol design. The entrance scores for dandruff and itching are low because the patients had just completed a year long study using the "old" shampoo.

i. Adherent dandruff - the maximum possible score is 5. The mean scores and % reduction from baseline are given.

Treatment Group		
Visit	"Old" Shampoo	"New" Shampoo
Baseline		
N	16	36
Mean Score	0.5	0.8
4 Weeks		
N	16	36
Mean Score %	0.3 (40%)	0.8 (0)

ii. Loose dandruff - the maximum possible score is 5.

Visit	"Old" Shampoo	"New" Shampoo
Baseline		
N	16	36
Mean Score	0.3	0.5
4 Weeks		
N	16	36
Mean Score	0.3 (0)	0.4 (20%)

iii. Total dandruff - the maximum possible score is 10.

Visit	"Old" Shampoo	"New" Shampoo
Baseline		
N	16	36
Mean Score	0.8	1.3
4 Weeks		
N	16	36
Mean Score %	0.6 (25%)	1.2 (8%)

iv. Itching - the maximum possible score is 4.

Visit	"Old" Shampoo	"New" Shampoo
Baseline		
N	16	36
Mean Score	0.2	0.3
4 Weeks		
N	16	36
Mean Score %	0.1 (50%)	0.2 (33%)

d. Safety Evaluation: There were no adverse reactions or reports of scalp erythema, irritation during the study.

Comment: This study has little value as a means of establishing the therapeutic equivalence of the products manufactured by two different methods. The baseline scores were so low that meaningful change is difficult to assess. The number of patients in the "old" shampoo group is very small and makes statistical analysis questionable.

Nevertheless, there is no reason to think that the described difference in manufacturing procedure will affect the efficacy of the drug product. The product to be marketed will be chemically identical to the product used in the pivotal clinical trials and must meet the same specifications as that product did. A study to accurately assess the relative efficacy of the "new" and "old" formulations would require hundreds of patients and is not justified by the circumstances.

B. Phase I Safety Studies and Safety Reviews

1. Study Title: A Protocol to Determine the Irritation Potential of Ketoconazole 1% Shampoo (J&J Protocol No. 16399.05)

Investigator: Howard Maibach, M.D.
Dermatology Research
San Francisco, CA

Method: This study was designed to compare the contact irritation and sensitization potential of ketoconazole 1% shampoo, Selsun Blue (1% selenium sulfide) Shampoo, and Head and Shoulders (1% zinc pyrithione) 2 in 1 Dandruff Shampoo.

The study consisted of a pre-test (5 day) period, a 21-day cumulative irritancy phase (induction phase), a 10 day rest

period, and a rechallenge of any patients who exhibited irritation reactions of grade 1 (on a scale of 0-4) during the cumulative irritancy study.

The pre-test phase was intended to determine the optimal dilutions of test products to be used during the cumulative irritancy phase. Because shampoos contain detergents, use of the full-strength products during standard patch testing would cause rather severe reactions in most test subjects.

Therefore, dilutions of 1%, 2.5%, 5% and 10% of the full strength products were tested. The results indicated that the 1% dilution was most appropriate.

During the indication phase, patches were applied to the right or left scapular area which contained 0.2 mL. of the test solutions. The patches were applied according to a randomization scheme so that the evaluator did not know which preparation was being scored. The patches were reapplied with fresh drugs 5 times weekly for 3 weeks (total 15 applications). Irritation was scored at each patch application on the following scale:

0	=	Negative
+	=	Equivocal reaction (0.5)
1	=	Erythema
2	=	Erythema and induration
3	=	Erythema, induration, and vesicles
4	=	Bullae

The maximum possible irritation score would be 1500 (25 subjects x score of 4 x 15 evaluations). Due to the irritation seen at some point during the course of the induction phase, it was decided to have the strength of the solution applied reduced (to 0.5%) in 2 subjects for ketoconazole, 4 subjects for Selsun Blue, and 3 subjects for Head and Shoulders. The scores obtained with the 1% and 0.5% dilutions were totaled in these instances.

In the challenge phase, test products were applied to new test sites on the back and occluded for 72 hours. Sensitization was evaluated and scored on the same scale as above.

Results: Twenty-six subjects entered the study (15 female, 11 male; 16 caucasian, 10 hispanic; mean age 44 years). One subject was discontinued by the investigator due to protocol violations. The remaining 25 completed the induction phase, and 22 of these returned for the challenge phase.

The following cumulative irritancy scores were found:

Product	Score
Ketoconazole	203
Selsun Blue	283
Head & Shoulders	291

In the challenge phase, there were numerous cases of speckled erythema which the investigator felt were due to irritation reactions rather than sensitization. There was one response by one subject to 0.5% Selsun Blue which the investigator scored as a grade 2 sensitization reaction.

Comment: This test enrolled fewer subjects than is preferable in an irritancy study (100 would be an optimum number). However, ketoconazole 1% shampoo did not demonstrate any unusual irritancy or sensitization potential in large-scale clinical testing (see above). In addition, under the conditions of this test it is comparable in cumulative irritancy to other widely used OTC shampoos. It is felt that further testing is not necessary.

2. Safety Update: The safety update submitted by the sponsor includes all safety data available through April, 1993. This review will separate the information between the 1% and 2% (Nizoral Shampoo) formulations.

I. 2% Shampoo

The Nizoral Shampoo clinical program included 11 clinical trials conducted in the U.S. and 8 clinical trials conducted in foreign countries.

In the U.S. clinical studies there were 9 adverse events which were probably or possibly related to drug use in 230 patients exposed to the drug (9/230 = 4%). One report of exfoliative dermatitis was evaluated as severe. Other reactions (4 reports of abnormal hair texture and one each of pruritus, dry skin, pustular rash and taste perversion) were evaluated as mild.

In addition, 5 children aged 3-5 and 11 infants were treated for tinea capitis and cradle cap. Two of these children had adverse events; one bacterial infection and one allergic reaction (treated with prednisone).

Since Nizoral Shampoo was approved in the U.S. in 1990, about million 4 oz. bottles have been sold. During this time, these have been 96 spontaneous adverse reaction reports concerning the drug. The following table (taken directly from the sponsor's submission) summarizes these reports.

Summary of Quarterly Adverse Experience Postmarketing Spontaneous Reports for Janssen NIZORAL 2% Shampoo Use in the U.S.	
System Organ Class Preferred term	Ketoconazole 2% Shampoo
Application Site Disorder	14
Application Site Reaction	11
Contact Dermatitis	3
Auto Nervous System Disorder	1
Flushing	1
Body as a Whole General Disorder	18
Allergic Reaction	2
Face Edema	1
Fever	1
Side Effect	3
Symptoms Aggravated	5
Therapeutic Response Decreased	6
Liver and Biliary System	2
Hepatic Function Abnormal	2[a]
Skin and Appendages Disorder	54
Alopecia	22
Dermatitis	1
Hair Discoloration	11
Hair Texture Abnormal	8
Pruritus	4
Psoriasis aggravated	1
Rash	2
Rash Erythematous	1
Rash Maculopapular	1
Rash Pustular	1
Skin disorder	2
Special Senses	5
Paroamia	1
Taste Perversion	4
Vision Disorders	2
Conjunctivitis	1
Vision Abnormal	1
a One subject showed elevations in alkaline phosphatase (204 IU/L) at a routine physical examination; other liver functions were normal and the subject was asymptomatic. One subject who used the shampoo on his chest and back had elevated LFTs during the course of therapy; this subject had abnormal LFTs prior to using the shampoo.	

The 3 "side effect" reactions under Body as a Whole General Disorder are complaints concerning hair texture (straightened hair which had been permed, etc.)

The adverse reaction rate per unit sold is million = 0.005%.

In foreign clinical trials with Nizoral shampoo, there were 7 adverse events in 172 subjects (7/172 = 4%). These included 4 hair texture abnormal, 1 hair loss, 1 irritation and 1 complaint of bad shampoo odor.

Since the first approval of Nizoral Shampoo in a foreign country in 1988, these have been approximately million containers sold. There have been 60 spontaneous adverse reaction reports since marketing began, summarized in the following table which was also taken directly from the sponsor's submission.

Summary on Non-U.S. Postmarketing Spontaneous Reports with Nizoral 2% Shampoo	
System Organ Class Preferred Term	Ketoconazole 2% Shampoo
Body as a Whole General Disorder	**10**
Allergic Reaction	3
Asthenia	1
Hot Flashes	1
Oedema	3
Oedema Periorbital	1
Pain	1
Endocrine Disorders	**1**
Adrenal Insufficiency	1
Gastrointestinal System Disorder	**5**
Abdominal Pain	1
Anorexia	2
Nausea	1
Vomiting	1
Skin and Appendages Disorders	**36**
Acne	2
Alopecia	1
Bullous Eruption	1
Desquamation	3
Eczema	1
Hair Discoloration	2
Hair Texture Abnormal	1
Photosensitivity	1
Pruritus	7
Rash	2
Rash Erythematous	8
Rash Maculopapular	2
Seborrhoea	3
Skin Disorder	1
Urticaria	1
Central & Peripheral Nervous System Disorder	**3**
Nervousness	1
Paraesthesia	2
Respiratory System Disorder	**1**
Rhinitis	1
Vision Disorder	**1**
Vision Abnormal	1
Application Site Disorder	**3**
Dermatitis Disorder	3

The adverse reaction rate per unit sold is million = 0.0003%.

NDA: 20-310

II. 1% Shampoo

The ketoconazole shampoo 1% clinical program (reviewed above) exposed a total of 583 patients to the drug. The adverse reactions which were probably or possibly related to treatment totaled 17 (17/583 = 3%). The following table summarizes these effects. It should be noted that the erythema/irritation evaluations which were included in the protocol are not listed here (the reactions noted below are spontaneous reactions).

Summary of Adverse Experiences in Ketoconazole 1% Clinical Trials	
System Organ Class	Number
Skin	
Acne	1
Application site reaction	2
Pruritus	3
Rash	3
Urticaria	2
Seborrhea	1
Special Senses	
Conjunctivitis	1
Eye Pain	1
Headache	1
Ear Pain	2
	17

The following table, which was taken directly from the sponsor's submission, summarizes all the adverse reactions seen in 1% ketoconazole shampoo patients, whether related to drug therapy or not .

APPENDIX B.2
Summary of All Adverse Events with J&J CPI Ketoconazole 1% Shampoo

Body System COSTART TERM	Ketoconazole 1.0%
Number of Exposures to Treatment[a]	660(100%)
Adverse Events by Exposure	200(30%)
Body as a Whole	64(10%)
Fever	1(<1%)
Flu Synd	14(2%)
Headache	46(7%)
Infec	3(<1%)
Pain	3(<1%)
Pain Back	1(<1%)
Cardiovascular	5(<1%)
Extrasystoles Vent	1(<1%)
Hypertens	1(<1%)
Migraine	1(<1%)
Pain Chest	1(<1%)
Sudden Death	1(<1%)
Tachycardia	1(<1%)
Digestive	23(3%)
Diarrhea	3(<1%)
Dyspepsia	1(<1%)
Dysphagia	1(<1%)
Gastritis	1(<1%)
Gingivitis	1(<1%)
Infect	1(<1%)
Jaundice Cholestat	1(<1%)
Pain	1(<1%)
Tooth Caries	2(<1%)
Tooth Dis	12(2%)
Endocrine	1(<1%)
Hypothr	1(<1%)
Hemic and Lymphatic	1(<1%)
Anemia	1(<1%)
Metabolic and Nutritional	3(<1%)
Gout	2(<1%)
Hypercholesterem	1(<1%)
Musculoskeletal	30(5%)
Arthralgia	2(<1%)
Arthritis	6(<1%)
Bone Fract Spontan	1(<1%)
Foot Surgery	1(<1%)
Injury Accid	6(<1%)
Joint Dis	1(<1%)
Myalgia	2(<1%)
Neck Rigid	1(<1%)
Pain	3(<1%)
Pain Back	5(<1%)
Pain Neck	2(<1%)
Tendon Dis	2(<1%)

APPENDIX B.2 (Continued)

Summary of All Adverse Events with J&J CPI Ketoconazole 1% Shampoo

Body System COSTART TERM	Ketoconazole 1.0%
Nervous System	1(<1%)
Nervousness	1(<1%)
Respiratory	95(14%)
Bronchitis	7(1%)
Cough Inc	2(<1%)
Dyspnea	1(<1%)
Infect	63(10%)
Pharyngitis	6(<1%)
Pneumonia	2(<1%)
Pneumothorax	1(<1%)
Rhinitis	5(<1%)
Sinusitis	19(3%)
Skin	17(3%)
Acne	1(<1%)
Applicat Site React	2(<1%)
Cyst	3(<1%)
Herpes Simplex	1(<1%)
Infect	1(<1%)
Pruritus	3(<1%)
Rash	4(<1%)
Seborrhea	1(<1%)
Trauma	1(<1%)
Urticaria	2(<1%)
Special Senses	8(1%)
Conjunctivitis	1(<1%)
Headache	1(<1%)
Otitis Med	1(<1%)
Pain Ear	4(<1%)
Pain Eye	1(<1%)
Urogenital	12(2%)
Dysmenorrhea	7(1%)
Elective Surgery	1(<1%)
Ham Vaginal	1(<1%)
Infect Urin Trac	1(<1%)
Mens Dis	1(<1%)
Vaginitis	1(<1%)

Ketoconazole 1% shampoo has been approved in 4 foreign countries, (Argentina, Colombia, Mexico, Thailand) beginning in 1989. About 4.9 million containers have been sold during this time, with no adverse reaction reports for this strength. In addition, six clinical trials have been performed in support of these overseas products, exposing a total of 118 patients. Two reports of abnormal hair texture were generated as a result of these trials.

3. Safety Summary The data submitted in support of this application justify the OTC marketing of the product in terms of safety. The adverse reaction rate seen in over 500 patients was about 3%, and the reactions seen were localized and reversible. No reactions were reported which appeared to be related to systemic toxicity.

When the patients were specifically examined periodically for erythema and irritation, 8/102 in the long-term study exhibited these reactions, most of which resolved spontaneously while therapy continued. In the 8-week pivotal study, 10/445 patients examined at week 8 had increased erythema/irritation (10/445 = 2%).

The small irritation/sensitization study submitted indicates that 1% ketoconazole shampoo is no more likely to cause these reactions than other popular OTC shampoos (or else was unable to detect differences because of the small number of patients treated).

Finally, experience with the already approved Nizoral Shampoo (2% ketoconazole) does not suggest an unusual pattern of toxicity, either in terms of frequency or severity of reactions reported.

There is no evidence presented of the relative safety of the use of this product in children.

C. Labeling Review. The label proposed by the sponsor requires revision. On the proposed front label, the claim
should be deleted. This claim is non-specific and unsubstantiated.

Rather than list individual criticisms of the proposed back label, a recommended version will be provided, as follows:

supervision for a disorder which has no serious health implications. Under these circumstances, it may be useful to present this application to the Dermatologic Drugs Advisory Committee and/or OTC Drugs Advisory Committee for further review.

David Bostwick

Wiley A. Chambers, M.D.

cc: Orig. NDA
HFD-520/Label File/DeSantis
HFD-520/Dep.Dir/Gavrilovich
HFD-520/SMO/Chambers
HFD-520/MO/Bostwick
HFD-520/Chem/Pappas
HFD-520/CSO/Cook
HFD-520
HFD-500
HFD-638
HFD-735
HFD-82

Supervisory Medical Officer - Comment
Final labeling review will be completed after consultation is received from Office of OTC Drug Products.

Medical Officer's Review of NDA 20-310
Amendment

NDA 20-310

Submission: 2/25/94
Review completed: 3/18/94

Proposed trade name:
Generic name: Ketoconazole 1% shampoo

Sponsor: Johnson & Johnson Consumer Products, Inc.

Proposed Indication(s): Controls the flaking, scaling and itching associated with dandruff

Submitted: Revised Labeling

Reviewer's Comments: *Labeling recommendations are identified below. Recommended deletions are identified by ~~single lines.~~ Recommended additions are identified by shading.*

Front Label:

Reviewer's Comments: *The name is not considered acceptable. Based on the Chemist's Review Comments, information on the 4 and 7 oz size containers have not been submitted for review.*

1 Page Deleted

Reviewer's Comments: *The location of the expiration date and the lot number should be specified.*

Safety and Efficacy Summary:

The applicant has been granted authorization to cross-reference NDA 19-927, Ketoconazole shampoo 2%, in support of the safety of this product.

Ketoconazole 2% includes labeling which limits the product's use to prescription only.

The applicant's efficacy studies support the effectiveness of ketoconazole shampoo, 1%. The dose comparison study fails to demonstrate a significant difference between the 1% and the 2% concentrations, however the power of the study to detect such a difference is considered low.

Reviewer's Comments:

This application currently contains a discrepancy in the safety profile.

If

a) the ketoconazole 1% application relies on the safety of the ketoconazole 2%;

b) the ketoconazole 1% and ketoconazole 2% products are considered equivalent in safety and efficacy based on the submitted information and

c) the ketoconazole 2% includes a prescription only restriction

then ketoconazole 1% should not have a OTC indication but should have a prescription only restriction. If the ketoconazole 2% prescription only labeling cannot be supported, then both products should be considered for OTC indications.

The sponsor of NDA 19-927, Ketoconazole shampoo 2% has been requested to provide an justification for the prescription restriction. The applicant for this NDA (20-310) should provide an explanation for any deviation in the labeling from NDA 19-927 because it was cross-referenced. Specifically, the applicant should provide a counter explanation to any justification for provided by the sponsor of NDA 19-927.

Recommendations:

1. NDA 20-310, Ketoconazole shampoo 1% as submitted and amended is **not recommended** approval.

2. The applicant must provide a justification for not following the labeling specified in NDA 19-927, Ketoconazole shampoo 2% and a counter explanation to any justification for prescription only marketing provided by the sponsor of NDA 19-927.

3. If the conditions listed in #2 are met, it is recommended that the labeling be revised as outlined above.

Wiley A. Chambers, M.D.
Supervisory Medical Officer

cc: HFD-540
HFD-340
HFD-540/CSO/Cook
HFD-540/CHEM/DeCamp
HFD-540/MICRO/Soprey
HFD-540/PHARM/Alam
HFD-540/MO/Chambers

See review by MO dated 1/24/96

Medical Officer's Review of NDA 20-310
Amendment

NDA 20-310

Submissions: 10/7/94, 12/14/94, 12/15/94, 12/19/94
Review completed: 1/24/96

Proposed trade name: Nizoral A-D
Generic name: Ketoconazole 1% shampoo

Sponsor: Johnson & Johnson Consumer Products, Inc.

Proposed Indication(s): Controls the flaking, scaling and itching associated with dandruff

Submitted: Response to clinical/regulatory deficiencies including a justification for marketing both a 1% and 2% concentration.

Background:

In the Medical Officer's review dated 3/18/94, non-approval of NDA 20-310, Ketoconazole shampoo 1% was recommended. It was further recommended that the applicant provide a justification for not following the labeling specified in NDA 19-927, Ketoconazole shampoo 2%.

7/19/94 Meeting and 10/7/94 Submission:

No safety issues have been identified to distinguish ketoconazole 1% and ketoconazole 2%. The applicant acknowledged that the products must be differentiated by their respective labeling.

Reviewer's Comments: *Concur. No safety issues have been identified which would differentiate the 1% from the 2% shampoos.*

12/8/94 Teleconference and 12/15/94 Submission:

Janssen (NDA Holder for NDA 19-927: Ketoconazole 2% shampoo) committed to supplementing NDA 19-927, for the treatment of tinea versicolor

Reviewer's Comments:

This action would differentiate the 2% ketoconazole product from the 1% ketoconazole product by virtue of the 2% only being indicated for an condition which must be diagnosed with the aid of a physician. The differentiation is considered acceptable from a clinical perspective.

12/91/94 Submission:

Johnson & Johnson Consumer Products acknowledged that the approval of NDA 20-310 would be coordinated with the
NDA 19-927.

Reviewer's Comments: *Acceptable.*

Labeling:

Based on multiple discussions and reviews within the agency, it is recommended that the labeling for ketoconazole 1% be revised to read as follows:

Front Label:

1 Page Deleted

Recommendations:

1. It is recommended that NDA 20-310, Ketoconazole 1% Shampoo with the labeling identified in this review be considered approvable at this time with final approval being dependent on
indication for ketoconazole 2%.

2. It is recommended that the applicant submit a safety update as required under 21 CFR 314.50(d)(5)(vi)(b).

Wiley A. Chambers, M.D.
Medical Officer

cc: NDA 20-310
NDA 19-927
HFD-540
HFD-340
HFD-540/CSO/Blatt
HFD-540/CHEM/Tso
HFD-540/MICRO/Soprey
HFD-540/PHARM/Alam
HFD-540/MO/Chambers

MAY 15 1997

MEDICAL OFFICER'S REVIEW OF AMENDMENT TO NDA 20-310

May 12, 1997

SPONSOR: Johnson & Johnson
Skillman, NJ

PRODUCT: Ketoconazole 1% shampoo

TRADE NAME: Nizoral A-D shampoo

CLINICAL INDICATION: Dandruff

DATE OF AMENDMENT: April 18, 1997

REASON FOR AMENDMENT: Revision of labeling

The labeling has been revised, and is now in accordance with that previously recommended by the reviewing medical officer.

Conclusions: The labeling is now acceptable, and the application is approvable.

Phyllis A. Huene, M.D.

cc: Orig NDA
HFD-540
HFD-540/Huene
HFD-540/Blay
HFD-540/Jacobs
HFD-540/DeCamp