

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20-310**\_\_\_\_\_

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

NDA: 20-310SUBMISSION DATE: Dec. 18, 1992

Ketoconazole 1% shampoo

BRAND NAME:

Johnson & Johnson Consumer Products, Inc.,  
 Grandview Road  
 Skillman, NJ 08558

REVIEWER: Funmilayo Ajayi, Ph.D.TYPE OF SUBMISSION: OTC product      CODE: 3, S

SYNOPSIS: NDA 20-310 was filed on December 18, 1992 for 1% ketoconazole shampoo as an OTC product proposed for the control of flaking, scaling, and itching associated with dandruff. The sponsor monitored the percutaneous absorption of ketoconazole from this preparation during a period of extensive application over 6 to 12 months. A 2% ketoconazole shampoo was approved in the USA in 1990 as a prescription product.

RECOMMENDATION: Based upon the review of the data submitted in the current NDA 20,310, NDA 19,927, and the literature, the Division of Biopharmaceutics support the approval of this product. However, labeling comment (pg 4) must be satisfactorily addressed.

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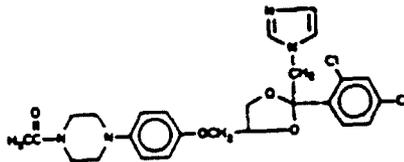
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ORGANIZATION OF REVIEW: Following the background is a description of the drug formulation. Thereafter is a summary of the studies followed by the general comments and comments to the Firm.

BACKGROUND: Ketoconazole (mol.wt. 531.44) is an imidazole antimycotic compound which causes non-specific inhibition of cytochrome P-450 enzymes. The inhibition of the P-450 may be fairly selective for the 3A isozyme at very low concentrations. The  $IC_{50}$  is 1  $\mu$ M (531 ng/ml). Results of studies in animals gave indication of strong binding to P-450 mono-oxygenase complex. It is extensively

metabolized in the liver to inactive metabolites which are mainly excreted in the faeces. The metabolism of ketoconazole is inducible by other drugs; and by ketoconazole itself at doses greater than 400mg/day (Brass *et al.*, 1982). It is 83.7% bound to plasma protein (mainly albumin), 15.3% bound to blood cells, and only 1% is present as free drug.

Structural formula



Molecular formula:  $C_{26}H_{28}Cl_2N_4O_4$   
Molecular weight: 531.44

**DRUG FORMULATION:**

The following is a tabulation of the components of the drug product.

| COMPONENT TRADE NAME     | COMMON NAME               | % SOLUTION | MANUFACT. COMPONENT % w/w | INGREDIENT % w/w |
|--------------------------|---------------------------|------------|---------------------------|------------------|
| Ketoconazole, USP        | Ketoconazole, USP         | N/A        |                           |                  |
| NF                       | Carbomer 1342, NF         | N/A        |                           |                  |
|                          | Sodium Laureth Sulfate    | 26%        |                           |                  |
|                          | Sodium Cocoyl Sarcosinate | 30%        |                           |                  |
|                          | Cocamide MEA              | N/A        |                           |                  |
|                          | Glycol Distearate         | N/A        |                           |                  |
| Butylated Hydroxytoluene | BHT                       | N/A        |                           |                  |
|                          | Tetrasodium EDTA          | 38%        |                           |                  |
|                          | Fragrance                 | N/A        |                           |                  |
|                          | Polyquaternium-7          | 8%         |                           |                  |
|                          | Quaternium-15             | N/A        |                           |                  |
| FD&C Blue No. 1          | FD&C Blue No. 1           | N/A        |                           |                  |
| Sodium Hydroxide, NF     | Sodium Hydroxide, NF      | N/A        |                           |                  |
|                          | Sodium Chloride           | N/A        |                           |                  |
| Purified Water, USP      | Purified Water, USP       | N/A        |                           |                  |
| Hydrochloric Acid, NF    | Hydrochloric Acid, NF     | N/A        |                           |                  |

\* Based on 95% dye purity. Adjust if certified purity is not 95%  
\*\* Sufficient to adjust pH to 7.0 - 7.3 (not to exceed 0.3% w/w total).  
\*\*\* Sufficient to adjust viscosity to 4,000-9,000 cps. (not to exceed 0.6% w/w total).  
\*\*\*\* Sufficient to adjust pH to 7.0 - 7.3.

## ANALYTICAL METHOD:

## SUMMARY OF STUDY:

A. The absorption of ketoconazole from the CPI 1% shampoo was investigated as part of a clinical study # 16399.41A. Subjects with dandruff (102) were enrolled in a long-term safety and efficacy study. They were to shampoo 4 to 10 times per week over a period of 12 months. Of this number, 48 (15 males, 33 females) had plasma level of ketoconazole determined during the 9th month. Ketoconazole was not detected in any of the 4 and 8 hour post application sampling times.

B. Cross-reference was made to NDA 19,927 for 2% Ketoconazole shampoo by Janssen Pharmaceutica Inc. One pharmacokinetics study (n=6) and 6 clinical studies (n=139) with plasma level determination were reported. The shampoo was applied 2-10 times per week. Overall, ketoconazole was not detected in any plasma samples obtained at various times after the application of the shampoo.

## GENERAL COMMENTS (NEED NOT BE SENT TO THE FIRM)

1. The sponsors (Janssen; Johnson & Johnson) for the 1% and 2% ketoconazole shampoo were unable to demonstrate percutaneous absorption of ketoconazole from the preparations following unrestricted use for periods ranging from 1 to 18 months. Though unproven, absorption from the shampoo (however low) can not be ruled out. The possible effect of low concentration of ketoconazole on the liver metabolizing enzymes is yet unclear.

2. The concentration of ketoconazole that will produce 50% inhibition of the P-450 enzymes ( $IC_{50}$ ) is ca  $1\mu M$  (531 ng/ml). This concentration is 106 times greater than the assay sensitivity (5 ng/ml) reported for the method employed in the studies.

3. Also, a published data revealed that the biochemical indices of liver function remained within normal range in all patients who have been taking 200 mg daily oral dose of ketoconazole for 1 to 6 months. In this study, the mean  $C_{max}$  was  $3.2\mu M/l$ ; while the mean  $C_{ss}$  was  $0.51\mu M/l$ .

4. The percutaneous absorption of ketoconazole following application of the shampoo in children was not studied. This information is important for an OTC product such as this.

5. Other findings from literature:

5.1 Reports following the use of 2% ketoconazole cream gave indication of plasma levels in adult patients below the limit of detection; or plasma levels in infants aged 1 to 5 months (mean 0.064  $\mu\text{g/ml}$ ) that were at least times less than the reported levels following oral dosing in adults ( $\mu\text{g/ml}$ ).

5.2 Similarly, percutaneous absorption from vaginal pessaries (400, 800, & 1200 mg doses) was found to be approximately 1% of each dose.

5.3 Drug accumulation was not observed in patients (n = 56) aged years on daily oral dosing of 200 mg ketoconazole for up to 7 months. The observed mean elimination  $t_{1/2}$  was 3.3h, and a negative correlation was observed between blood level and age. Due to the fact that ketoconazole is extensively metabolized in the liver, the authors thought that the above finding might be indicative of the possibility of a lower capacity for the metabolism of ketoconazole in the young.

COMMENTS TO FIRM:

In view of the fact that percutaneous absorption of this product has not been studied in children, coupled with the larger percent of the total body surface area that will be exposed following application in children, unprescribed use of the product in children below the age of 12 years should be restricted.

5/10/93

Funmilayo O. Ajayi, PhD  
Pharmacokinetics Evaluation Branch

Biopharm Day (Ludden, Malinowski, Hunt, Ajayi)

*for*

FT initialed by Nicholas Fleischer, PhD .....

5/12/93

cc: NDA 20-310, HFD-520 (Clinical Division), HFD-426 (Fleischer, Ajayi), Chron, Drug, Reviewer, FOI (HFD-19), GA.

**APPENDIX I**

AN EVALUATION OF THE SAFETY IN LONG-TERM USE AND EFFICACY OF AN ANTI-DANDRUFF SHAMPOO

STUDY #: 16399.41A      VOLUME: 1.8 & 1.11, Pg 249-298

INVESTIGATOR AND LOCATION:

OBJECTIVE: To evaluate the long-term safety of an anti-dandruff shampoo in a population having dandruff, plus efficacy as measured against baseline dandruff; as well as to determine the plasma level of ketoconazole in samples from volunteers during the study.

FORMULATION: 1% ketoconazole shampoo; CPI formula 1760-156 Lot #s P1-055, P1-112, P-185, and 0061P.

STUDY DESIGN: Non-crossover, open-label study with all subjects on a single treatment regimen (4-10 times use of shampoo per week).

SUBJECTS: 102 subjects; 48 (15 males; 33 females) of this number had blood samples withdrawn at the 9th month of treatment for determination of plasma concentration of Ketoconazole.

SAMPLING: Blood samples were drawn at the 9th month of treatment. 20 subjects had blood withdrawn 4h after using the shampoo; while 28 had blood withdrawn 8h post application of shampoo.

ASSAY:

Linearity:                was proved between                                ng/ml.  
Sensitivity:              The limit of detection is                                ng/ml.  
                              The limit of quantitation                                ng/ml.  
Specificity:              Satisfactory.  
Accuracy:                % accuracy is 97 for range                                ng/ml.  
Precision:                %CV varied from 2 to 9 for range                                ng/ml.

RESULTS: An attempt was made to determine the concentration of ketoconazole in the plasma samples. The concentration of ketoconazole was below the detection level in all the samples.

CONCLUSION: Ketoconazole was not detected in any of the samples. Percutaneous absorption following unrestricted use was reported to be minimal.

COMMENTS: Cross-reference was made to NDA 19,927 for the approved Janssen's 2% ketoconazole shampoo. Reports in the approved NDA indicated that ketoconazole was not detected (assay sensitivity ng/ml) in any of the plasma samples from 7 studies (n=139).

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TABLE I  
Summary of Studies

| Protocol Number-Investigator  | Report Date   | Study Design  | Duration of Treatment  | Treatment and Dosage                     | Number of Treated Subjects | Number of Subjects With Plasma Determinations |
|---|---------------|---|------------------------|--|----------------------------|---|
| <b>Clinical Study With Ketoconazole 1% Shampoo</b>  |               |   |                        |  |                            |   |
| 16399.41A-Kantor  | October 1992  | Single-center, open-label, long-term study of safety and efficacy in subjects with dandruff                             | 12 months <sup>a</sup> | ketoconazole 1.0% (CPI Formula 1760-156) | 102 <sup>b</sup>           | 48  |
| <b>Pharmacokinetic Study With Ketoconazole 2% Shampoo</b>                                 |               |   |                        |  |                            |   |
| R41,400/152-Van Peer Gasparini Van de Velde Woestenborghs Van Cutsem Heykants Cauwenbergh | June 1986     | Open-label, non-comparative, eight-week safety study in volunteers  | 8 weeks                | ketoconazole 2.0% (Janssen Formulation)  | 6                          | 6   |
| <b>Foreign Clinical Study With ketoconazole 2% Shampoo</b>                                |               |   |                        |  |                            |   |
| R 41,400/170-Van Lint De Doncker Woestenborghs  | June 1987     | Open-label, non-comparative, long-term study in subjects with moderate to severe dandruff and/or seborrheic dermatitis. | 3-26 months            | ketoconazole 2.0% (Janssen Formulation)  | 33                         | 33  |
| <b>U.S. Clinical Studies With Ketoconazole 2% Shampoo</b>                                 |               |   |                        |  |                            |   |
| JRD 41,400/508-Hickman  | January 1988  | Double-blind, placebo-controlled evaluation in subjects with moderate to severe dandruff.                               | 4 weeks                | Ketoconazole 2.0% (Janssen Formulation)  | 43                         | 37  |
| JRD 41,400/511-Hickman  | February 1988 | Open-label, long-term study of safety in subjects with moderate to severe dandruff.                                     | 6 months               | Ketoconazole 2.0% (Janssen Formulation)  | 24                         | 22  |

a Plasma data presented for this long-term study were collected at Month 9 only.

b All subjects were previously treated with either vehicle placebo, or ketoconazole 0.3%, 1%, or 2% shampoo for eight weeks in study 16399.41 (see section 7.4 of this NDA).

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| TABLE I<br>Summary of Studies (continued)                    |               |  |                       |   |                            |   |
|--|---------------|--|-----------------------|---|----------------------------|---|
| Protocol Number- Investigator                                | Report Date   | Study Design   | Duration of Treatment | Treatment and Dosage                    | Number of Treated Subjects | Number of Subjects With Plasma Determinations |
| U.S. Clinical Studies with Ketoconazole 2% Shampoo continued |               |  |                       |   |                            |   |
| JRD 41,400/512-Hickman                                       | March 1992    | Open-label, long-term study of safety in subjects with dandruff or seborrheic dermatitis. All subjects were previously treated for six months in 41,400/511                    | 12 months             | ketoconazole 2.0% (Janssen Formulation) | 18                         | 18  |
| JRD 41,400/513-Huebner                                       | February 1988 | Open-Label, long-term study in subjects with dandruff  | 6 months              | ketoconazole 2.0% (Janssen Formulation) | 16                         | 16  |
| JRD 41,400/514-Huebner                                       | March 1992    | Open-label, non-comparative, long-term safety study in subjects with dandruff and/or seborrheic dermatitis. All subjects were previously treated for six months in 41,400/513. | 12 months             | ketoconazole 2.0% (Janssen Formulation) | 13                         | 13  |

**APPENDIX II**

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Proposed Labelling

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**APPENDIX III**

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### 2.3            **MARKETING HISTORY**

JOHNSON & JOHNSON CPI does not currently market ketoconazole 1% shampoo in the United States or any foreign countries. Ketoconazole shampoo (NIZORAL®) has been successfully marketed worldwide by Janssen Pharmaceutica, Inc. since 1987 as both a prescription (2%) and as an over-the-counter shampoo (2% and 1%) for the treatment of the symptoms of dandruff in 69 countries, 33 of which also have an indication for seborrheic dermatitis of the scalp. In 1990, NIZORAL (2%) was approved in the United States for prescription use for the reduction of scaling due to of dandruff. Worldwide, between 1988 and mid-1992, total sales of ketoconazole calculated as units of 100 ml at a 2% concentration, was approximately

NIZORAL® shampoo has not been withdrawn from marketing in any country for any reasons.

A list of the countries in which ketoconazole shampoo is currently marketed is as follows:

**NIZORAL 1% Shampoo for the treatment of dandruff is marketed in:**

Argentina (OTC) -  
Mexico (OTC & Rx)  
Thailand (OTC)  
Colombia (Rx)

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**NIZORAL® 2% Shampoo for the treatment of dandruff is marketed in:**

OTC

Austria  
Belgium  
Brazil  
Costa Rica  
Cyprus  
Dominican Republic  
Finland  
Germany  
Luxembourg  
Iran  
Jamaica  
Kenya  
Kuwait  
Mexico  
New Zealand  
Oman  
Panama  
Philippines  
Saudi Arabia  
Singapore  
South Africa  
South Korea  
Thailand  
Trinidad  
UAE  
Uruguay

Prescription

Argentina  
Bahrain  
Burundi  
Canada  
Chile  
Colombia  
Denmark  
Ecuador  
El Salvador  
France  
Greece  
Guatemala  
Honduras  
Hong Kong  
Hungary  
Iceland  
India  
Indonesia  
Ireland  
Iraq  
Israel  
Italy  
Jordan  
Liberia  
Malaysia  
Netherlands  
Netherlands Antilles  
Norway  
Pakistan  
Poland  
Portugal  
Qatar  
Spain  
Sri Lanka  
Sweden  
Switzerland  
Taiwan  
Turkey  
U.K.  
U.S.A.  
Venezuela  
Yugoslavia  
Zambia

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NIZORAL® with the additional indication for the treatment of Seborrheic Dermatitis is marketed in:

Argentina  
Austria  
Belgium  
Brazil  
Canada  
Chile  
Colombia  
Denmark  
Finland  
France  
Germany  
U.K.  
Holland  
Iceland  
India  
Indonesia  
Ireland  
Israel  
Italy  
South Korea  
Mexico  
New Zealand  
Norway  
Philippines  
Portugal  
Saudi Arabia  
South Africa  
Spain  
Sweden  
Switzerland  
Thailand  
Uruguay  
Venezuela

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