CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-310

PHARMACOLOGY REVIEW(S)

MAY 8 1997

Evaluation of Pharmacology and Toxicology Data
Division of Dermatologic and Dental Drug Products, HFD-540

NDA No.: 20-310 BL

Date Submitted: 4/18/97
Date CDER Received: 4/21/97
Date Assigned: 5/7/97
Date Review Completed: 5/7/97

Name of Drug: Nizoral A-D® (ketoconazole) 1% shampoo
cis-1-acetyl-4-[4-[[2-(2,4-di-chlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl] methoxy] phenyl] piperazine

Pharmacological Category: antifungal

Sponsor: Johnson and Johnson Consumer Products, Inc.
Skillman, NJ 08558-9418

Indication: dandruff

Route of Administration: topical

Related INDs/NDAs:

NDA 19-927	ketoconazole 2% shampoo	Janssen Research Foundation

INTRODUCTION

The present submission is a copy of the final labeling copy for the approvable product. No new Pharmacology/Toxicology studies were submitted in connection with this NDA. For a review of related nonclinical studies, please refer to the Pharmacology/Toxicology review of the original submission for NDA 19-927.

SUMMARY

Previously reviewed studies (Janssen) in animals with ketoconazole revealed no detectable percutaneous absorption of up to 50 mg/kg of the drug on intact or abraded skin in rabbits. According to the label for ketoconazole 2% shampoo, there was also no detectable drug in plasma samples examined from human patients. According to a Biopharmaceutics review dated 5/10/93, there has also been no detectable drug in the plasma of patients treated with the ketoconazole 1% shampoo that is the subject of this application. No pharmacokinetic assessment was made in pediatric patients in that study; the reviewer recommended that the label state that the product was not for use in children under the age of 12 years. The label includes a statement that the product should not be used in children under 12 years of age without first consulting a physician.

Ketoconazole 2% shampoo did not produce evidence of dermal irritation, dermal sensitization, or systemic toxicity when applied to rabbits for 1 hour daily for up to 6 months. When ketoconazole 1% shampoo (Janssen) was applied to rabbit skin under occlusion, it was a moderate irritant. Vehicle and ketoconazole 1% shampoo were ocular irritants, but shampoo diluted to 0.3% was not. The label does state that the user should avoid contact of the shampoo with the eyes and that if that happens, the eyes should be rinsed thoroughly with water. This adequately addresses the issue of ocular irritation.

Ketoconazole was negative in systemic carcinogenicity studies and in genotoxicity studies. Ketoconazole is known to be teratogenic in rats when fed at 80 mg/kg/day. The label advises consulting a health professional before using the product if the user is pregnant or nursing.

CONCLUSIONS

From a pharmacology/toxicology standpoint, the submitted label is acceptable.

5/8/97

Amy C. Nostrandt, D.V.M., Ph.D.
Pharmacologist/Toxicologist

cc:
NDA 20-310
HFD-340
HFD-540
HFD-540/PHARM/Nostrandt
HFD-540/TLPHARM/Jacobs
HFD-540/MO/Huene
HFD-540/CHEM/Pappas
HFD-540/PMS/
C:\wpfiles\nda\n20310bl.wpd

Concurrence Only:
HFD-540/DD/WILKIN 5/15/97
HFD-540/TLPHARM/JACOBS 5/8/97

Review and Evaluation of Pharmacology and Toxicology Data
Division of Anti-Infective Drug Products, HFD-520

Date CDER Received: 12/21/92
Date Assigned: 12/28/92
Date Review Started: 12/30/92
Date 1st. Draft Completed: 12/31/92
Date Review Accepted by Supervisor: 1/4/93

NDA # 20-310 (Original Submission dated 12/18/92)

Number of Volumes: 3 (1.2 and 1.3 for composition of the formulation; 1.7: Pharm/Tox)

Drug: Ketoconazole 1% Shampoo.
Trade Name: Not specified

Sponsor: Johnson & Johnson Consumer Products, Inc., Skillman, NJ

Contact Person: Ms. Deborah L. Norby; 908/874-1434

Category: Antifungal Shampoo.

Indication: Control of flaking, scaling, and itching associated with dandruff; intended to be marketed as an over-the-counter (OTC) product.

Chemistry: see ketoconazole; CAS No. 65277-42-1

Formulation: Formulation Reference # 1750-156

Ingredient (Common Name)	% w/w
Ketoconazole	1.000
(Carbomer 1342)	
(Sodium Laureth Sulfate)	
(Sodium Cocoyl Sarcosinate)	
(Cocamide MEA)	
Butylated Hydroxytoluene (BHT)	
(Tetrasodium salt of EDTA)	
(Fragrance)	
(Polyquaternium-7)	
(Quaternium-15)	
FD&C Blue No. 1	
Sodium Hydroxide	
Sodium Chloride	
Hydrochloric Acid	
Purified Water	

* Based on 95% dye purity.
** Sufficient to adjust pH to 7.0 - 7.3.
*** Sufficient to adjust viscosity to 4,000 - 9,000 cps.
**** Sufficient to adjust pH to 7.0 - 7.3.

IND	Ketoconazole Shampoo 2%	Janssen
IND	Ketoconazole Shampoo 1%	J & J CPI
NDA	Ketoconazole (Nizoral) Shampoo 2%	Janssen

Review Objectives: Review preclinical data with regard to safety for marketing of the drug.

Index of Studies: No preclinical were submitted in the NDA. However, they were incorporated by reference to NIZORAL (ketoconazole) 2% Shampoo (NDA 19-927).

TOXICOLOGY:

Ketoconazole Toxicity Studies (for marketing tablets for oral use. (submitted to NDA 19-927)

Table 1: **Ketoconazole Toxicity Studies (for marketing authorization of the tablets for oral administration)**

Type of Study	Species	Route	Duration
Acute Toxicity	Mouse	Oral, IV	14 days
	Rat	Oral, IV, IM	14 days
	Dog	Oral, IV	14 days
Subchronic and Chronic Toxicity	Rat	Oral	3, 6, 18 months
	Dog	Oral	12 months
Reproduction			
Fertility	Rat	Oral	Not applicable
Embryotoxicity	Rat	Oral	Not applicable
and Teratogenicity	Rabbit	Oral	Not applicable
Peri- and Postnatal	Rat	Oral	Not applicable
Mutagenicity			
Point and Gene Mutations			
Ames Test	Salmonella	In Vitro	
Drosophila Test	Drosophila	Oral	
HGPRT* Test	Hamster V79	In Vitro	
Chromosome Anomalies			
Chromosomal Aberrations Test	Human Lymphocytes	In Vitro	
Micronucleus Test	Rat	Oral	
Dominant Lethal Test	Mouse	Oral	
Transformation	Mouse Fibroblasts	In Vitro	
Carcinogenicity	Mouse	Oral	18 months
	Rat	Oral	24 months

* Hypoxanthine-guanine phosphoribosyl transferase

Ketoconazole Shampoo 2%: This formulation was the subject of NDA 19-927, The following toxicity studies (tabulated below) were submitted in NDA 19-927 were incorporated by reference.

Acute Systemic Toxicity of Ketoconazole 2% Shampoo

Table 2: Summary of Acute Systemic Toxicity of Ketoconazole 2% Shampoo.

Species (reference)	Route of Administration	Sex	Approximate LD_{50}	
			in mg Ketoconazole/kg	in ml 2% Shampoo/kg
Mouse (3)	Oral	M/F	300	15
Rat (4)	Oral	M/F	200	10

M = male, F = female

Topical Irritation Studies with Ketoconazole 2% Shampoo

Table 3: Topical Irritation Studies with Ketoconazole 2% Shampoo in Rabbits.

Type of Study (reference)	Site of Application	Duration of Observation	Daily Dosage of 2% Shampoo	Duration of Treatment
Primary Dermal (5)	Dermal (occlusive)	7 days	0.3 ml	Single Dose
Primary Eye (6)	Ocular	14 days	0.1 ml	Single Dose
Primary Eye (7)	Ocular	7 days	0.1 ml of 15% solution	Single Dose
Subchronic Dermal (8)	Dermal (semi-open)	28 days	0.1 , 1, 2.5 ml/kg (2, 20, 50 mg/kg)	28 days
Chronic Dermal (9)	Dermal (semi-open)	6 months	0.1, 1, 2.5 ml/kg (2, 20, 50 mg/kg)	6 months

Ketoconazole Shampoo 1%: Three studies (listed below), using the 1% formulation # 1126-77 [not # 1750-156 which is proposed for marketing in the present NDA # 20-310], and which were submitted in NDA 19-927 were incorporated by reference. (see reference # 11, 12, and 13 cited in NDA 20-310 Vol. 7, pages 000-00016 and -17). Results of these studies are appended (see Appendices 1-3)

1. Primary dermal irritation studies in rabbits.

2. Primary eye irritation studies in rabbits.

3. 28-Day subchronic dermal toxicity studies in rabbits.

Reviewer's Comments: Since different formulations (# 1116-77) rather than formulation (# 1760-156) proposed for marketing of the ketoconazole 1% shampoo was employed in the above noted toxicity studies, the composition of the two formulations was compared (see Appendix 4). The sponsor states:

> " The differences between Formula 1116-77 and Formula 1760-156 consisted of only minor changes in excipients. Stability studies conducted on this formulation (Formula 1760-156) demonstrated that the changes did not affect the physical or chemical stability of the ketoconazole 1% shampoo. Based on these findings, it was determined that the data obtained from the toxicology and ADME studies performed with the NIZORAL ketoconazole 2% shampoo and the early formulation (1985) of the ketoconazole 1% shampoo (Formula 1116-77) would be acceptable for the current ketoconazole 1% shampoo..."

ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION (ADME) STUDIES:

Rabbits: Dermal absorption of ketoconazole 2% shampoo in a 28-day dermal irritation study in rabbits. After 28 days of daily application of the shampoo at dose levels of 2, 20, or 50 mg/kg of ketoconazole on intact and abraded skin, a 5 ml blood sample was taken for the analysis of ketoconazole. Plasma concentrations of ketoconazole were determined by

The detection limit of the assay was ng/ml.

Ketoconazole was not detectable (below ng) in the plasma sample of any rabbit, including the high dose (50 mg/kg).

Dogs: Ketoconazole 2% cream was applied dermally on the depilated skin of beagle dogs. No measurable ketoconazole levels (detection limit: ng/ml) occurred in the plasma of the dogs treated daily for 28 days with 2% ketoconazole cream at a dose of 7 mg/kg/day.

Comments:

1. The active ingredient, ketoconazole, is currently approved and marketed for systemic as well as topical use. NIZORAL (ketoconazole) 2% shampoo is also currently approved as a prescription drug.

2. The present NDA is for a lower (1%) concentration of ketoconazole shampoo, but the applicant requests to market it as an ***over-the-counter (OTC) drug product.***

3. The currently approved and marketed product [NIZORAL (ketoconazole) 2% shampoo] is categorized as Pregnancy Category in the labelling.

Recommendation:

While I see no objection from a safety standpoint to the approval of this drug, the question of whether a drug with Pregnancy Category in the labelling could be marketed as an OTC drug product must be decided upon by appropriate Center personnel.

Appendices-4
Pharm/Tox Review of NDA 19-927

S.R. Joshi, D.V.M., Ph.D.

cc:
Orig. NDA
HFD-340
HFD-520
HFD-502/Osterberg
HFD-520/Pharm/Joshi
HFD-520/MO/Alpert
HFD-520/Chem/Tso
HFD-520/Micro/Sheldon
HFD-520/CSO/Cook
HFD-520 /rd init. by REOsterberg 1/6/94
RD/12/31/92/FT/1/5/93/SRJ
N-20-310 1/11/93

Concurrence Only:
HFD-520/DepDir/LGavrilovich
HFD-520/SPharm/REOsterberg

Table 12: Results of the Primary Dermal Irritation Study on Rabbits with Ketoconazole 1% and 15% Shampoo Under Occlusive Patch.(11)

	No. of Rabbits	Mean Score of Erythema and Eschar Formation	Mean Score of Edema Formation
Ketoconazole 1% Shampoo			
Intact Skin 24 h	6	2.8	2.5
Intact Skin 72 h	6	2.8	1.8
Abraded Skin 24 h	6	2.7	2.3
Abraded Skin 72 h	6	2.5	1.7
Subtotal		10.8	8.3
Sum of Mean Scores: 19.1 PDI Index: 4.8 Classification: Moderate Irritant			
Ketoconazole 15% Solution			
Intact Skin 24 h	6	1.7	1.5
Intact Skin 72 h	6	0.5	0.2
Abraded Skin 24 h	6	1.8	1.0
Abraded Skin 72 h	6	0.6	0.2
Subtotal		4.6	2.9
Sum of Mean Scores: 7.5 PDI Index: 1.9 Classification: Mild Irritant			
Placebo			
Intact Skin 24 h	6	2.3	2.2
Intact Skin 72 h	6	2.2	1.2
Abraded Skin 24 h	6	3.0	2.8
Abraded Skin 72 h	6	3.0	2.2
Subtotal		10.5	8.4
Sum of Mean Scores: 18.9 PDI Index: 4.7 Classification: Moderate Irritant			
Placebo 15% Solution			
Intact Skin 24 h	6	2.3	1.8
Intact Skin 72 h	6	1.0	0.7
Abraded Skin 24 h	6	2.2	1.3
Abraded Skin 72 h	6	1.3	0.5
Subtotal		6.8	4.3
Sum of Mean Scores: 11.1 PDI Index: 2.8 Classification: Moderate Irritant			

Table 13: Results of the Primary Ocular Irritation Study with Ketoconazole 1% Shampoo (undiluted and diluted).(12)

Parameters	Undiluted Shampoo		Diluted Shampoo (15%)	
	No. of Reacting Rabbits		No. of Reacting Rabbits	
	Ketoconazole 1%	Control	Ketoconazole 1%	Control
Cornea	6/6	6/6	0/6	0/6
Iris	3/6	3/6	0/6	0/6
Conjunctiva	5/6	6/6	0/6	0/6
Subject Rating	Positive	Positive	Negative	Negative

Table 14: Results of the Subchronic (28 Days) Dermal Irritation Study in Rabbits with Ketoconazole 1% Shampoo.(13)

Parameters	Males					Females				
	Mg Ketoconazole/kg/Day					Mg Ketoconazole/kg/Day				
	Saline Control	Vehicle Control	2	20	50	Saline Control	Vehicle Control	2	20	50
Mortality (Drug-related)	0/4 (0/4)	0/4 (0/4)	0/4 (0/4)	0/4 (0/4)	0/4 (0/4)	1/4 (0/4)	0/4 (0/4)	0/4 (0/4)	0/4 (0/4)	0/4 (0/4)
Clinical Observations (Skin & Ocular)	N	N	N	N	N	N	N	N	N	N
Body Weight	N	N	N	N	N	N	N	N	N	N
Urinalysis	N	N	N	N	N	N	N	N	N	N
Hematology	N	N	N	N	N	N	N	N	N	N
Serum Analysis	N	N	N	N	N	N	N	N	N	N
Organ Weight	N	N	N	N	N	N	N	N	N	N
Gross Pathology	N	N	N	N	N	N	N	N	N	N

N = within normal limits and/or comparable with controls.

Composition of Shampoo Formulations

Composition of Shampoo Formulations (% w/w)			
	Ketoconazole 2% Shampoo NIZORAL Formula	Ketoconazole 1% Shampoo Formula 1116-77	Ketoconazole 1% Shampoo Formula 1760-156
/Ketoconazole, USP /Sodium Laureth Sulfate /Sodium Cocoyl Sarcosinate /Cocamide MEA	2.1	1.0	1.0
/Sodium Chloride U.S.P. /Fragrance			
/Tetrasodium EDTA /Quaternium-15 /Polyquaternium-7			
/FD & C Blue No. 1			
/Glycol Distearate			
/Butylated Hydroxytoluene U.S.P. /Sodium Hydroxide N.F.			
/Hydrochloric Acid/Sodium Hydroxide q.s. to pH /Purified Water U.S.P.	%		

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 19-927 (Original Submission, dated December 15, 1988)

DATE RECEIVED: December 20, 1988

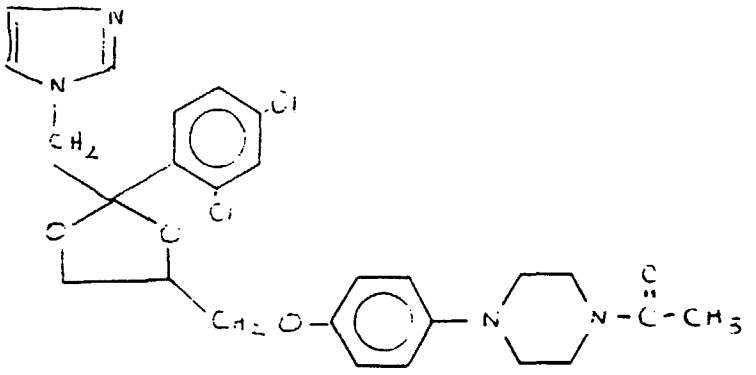
DATE ASSIGNED: December 27, 1988

DATE REVIEW COMPLETED: February 10, 1989

SPONSOR: Janssen Research Foundation
40 Kingsbridge Road
Piscatway, NJ 08855-3998

DRUG: Nizoral^{R} (ketoconazole) 2% Shampoo
R 41400

CHEMICAL STRUCTURE:



Cis-1-acetyl-4[4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1, 3-dioxolan-4-yl]methyl]phenyl]-piperazine

COMPOSITION:

Ingredient	Per gram	% w/w
✓Ketoconazole (microfine grade)	mg*	
✓ Sodium lauryl ether sulphate	mg	
✓Disodium monolauryl ether sulfosuccinate	mg	
✓Coconut fatty acid diethanolamide	mg	
✓Laurdimonium hydrolyzed animal collagen	mg	
✓Macrogal 120 methyl glucose dioleate	mg	
✓Imidurea	mg	
✓Perfume bouquet	mg	
Purified Water q.s. ad	mg g	%

* 5% overage added to assure the shelf life of 24 months.

CATEGORY: Antifungal agent

PROPOSED CLINICAL STUDIES OR MARKETING INDICATION:

The intended use of the shampoo is for the relief of symptoms associated with dandruff and seborrheic dermatitis of the scalp.

RELATED DRUGS/INDs/NDAs:

IND
NDA 18-533 Nizoral (ketoconazole) 200 mg Tablet, Janssen
NDA 19-084 Nizoral (ketoconazole) 2% Cream, Janssen

Other INDs for ketoconazole include the following:
IND
IND
IND
IND
IND
IND

PRECLINICAL STUDIES:

This submission contains the following preclinical studies; some have been previously submitted to IND

Pharmacology: Vol. 1.3

a.) Van Cutsem, J. The Antifungal Activity of Ketoconazole. Amer. J. Med., 74 (1B), 9-15 (1983)

b.) Borgers, M., and Van Cutsem, J. Ketoconazole-induced morphologic changes in yeasts and dermatophytes. In: "Oral Therapy in Dermatomycoses: a Step Forward", The Medicine Publishing Foundation Symposium Series No. 16 (1985), pp. 51-60.

Toxicology: Vols. 1.3 - 1.5

a.) Acute oral toxicity of 2% shampoo.

b.) Primary dermal irritation study of 2% shampoo in rabbits.

c.) Ocular irritation study of 2% and 0.3% shampoo in rabbits.

d.) 28-Day dermal irritation study in rabbits using 1% and 2% shampoo.

e.) 28-Day dermal irritation study in rabbits with partially degraded 2% shampoo.

f.) Primary dermal irritation study of 1% and 0.15% shampoo in rabbits.

g.) 6-Month dermal toxicity study in rabbits.

h.) Dermal absorption of the 2% shampoo in rabbits.

PHARMACOLOGY:

Ketoconazole is classified as a brood spectrum synthetic antifungal agent which inhibits the growth of a number of common dermatophytes and yeasts. Plasma membrane and cell wall changes occur together with an increase in the cell volume in the presence of ketoconazole. The mechanism of action of the drug is assumed to be the inhibition of the conversion of lanosterol to ergosterol, specifically by inhibiting the 14 α demethylase, which results in an increase in the accumulation of 14-methylsterols.

Ketoconazole is sporicidal and fungicidal against Pityrosporum ovale which is a lipophilic yeast abundant in sebaceous areas and assumed to be involved in seborrheic dermatitis.

ACUTE TOXICITY:

The results of acute toxicity studies with a 2% ketoconazole shampoo follow:

Species	Route	Approximate LD 50 (7 Day)
Mouse	oral (gavage)	15 ml/kg (300 mg/kg)
Rat	oral (gavage)	10 ml/kg (200 mg/kg)

The 2% shampoo used was not the exact formulation of the proposed marketed drug. Mice developed a decrease in general activity and diarrhea. All deaths (3/5 M, 2/5 F) occurred by Day 1. Surviving mice were asymptomatic by Day 3. In rats, all deaths (3/5 M, 2/5 F) occurred by Day 2. A decrease in general activity, diarrhea, and a slight vocalization when touched resulted. Fluid was observed around the nose and mouth the day of dosing.

SUBACUTE/CHRONIC TOXICITY:

Rabbit: 28 Day Dermal Irritation Study: No. 1683

Compound: R 41400, Batch No. F0801
Formulation: 2% Shampoo
Route: Dermal
Dose Levels: Saline control, VC, 2, 20, 50 mg R 41400/kg/day X 28.
Strain: NZW
Number: 4/sex/dose
Control Treatment: Placebo shampoo and physiological saline
Study Site: Janssen Pharmaceutica, Beense, Belgium
GLP/QAU Statements: Both present, Vol. 1.3, p 00-00125

The 2% Shampoo was applied to the clipped skin (abraded and intact) for one hour each day for 28 days. The volumes were 0.1 ml (2 mg/kg), 1 ml (20 mg/kg), and 2.5 ml (50 mg/kg). The study included clinical signs, body weight, food consumption, drug plasma levels, hematology, blood chemistry, organ weights, and gross and histopathology.

Results: One VC and one low dose rabbit died (week 4 and week 2, respectively) - no clinical signs due to drug application - normal body weight gain and food consumption-decrease ($p < 0.05$) WBC week 4, mid dose - significant changes occurred at week 4 in serum K (↑ low and mid dose), chloride (↑ mid dose), glucose (↑ low and high dose), triglycerides (↑ mid dose), creatinine (↑ low and high dose), total bilirubin (↑ mid dose), GGT(↑ low and mid dose) when compared to control - organ weights that were significant were the pancreas (↓ low dose, absolute), kidneys (↓ high dose, relative and absolute), thymus (↓ high dose absolute), thyroids (↑ mid dose relative and absolute) when compared to control - no dose related gross or histopathology was seen on exposed abraded or intact skin - drug plasma levels not detected when sampled two hours after last application day 28 (detection limit was 5 ng/ml using HPLC).

Discussion: There appeared to be no treatment related adverse effects from the drug or from the placebo shampoo. The hematology and blood chemistry changes that occurred appeared not to be treatment related.

Rabbit: 28-Day Dermal Toxicity Study: No. 2052

Compound: R 41400 Batch Nos. 88D26/F35 and 88C31/F35
Formulation: 2% Shampoo
Route: Dermal
Dose Levels: 50 mg/kg non-degraded ketoconazole
45 mg/kg 10% degraded ketoconazole
Strain: NZW
Number: 5/dose/sex
Study Site/Date: Janssen Pharmaceutica, Beerse, Belgium/July 1988
GLP/QAU Statements: Both present, Vol. 1.5, p. 00-00002

This study was done to evaluate the irritation potential of the 2% shampoo containing 10% degraded ketoconazole and compare it with non-degraded ketoconazole. The rabbits were exposed dermally 1 hour/day, five days/week to 2.5 ml of the shampoo, corresponding to 45 or 50 mg of the drug.

Results: No adverse effects were reported for either group of rabbits. Histopathologic examinations were not done on exposed skin or body organs, since no irritation was observed on the skin and no hematology or blood chemistry parameters were abnormal.

Rabbit: 28-Day Dermal Irritation Study: No. 1849

Compound: R 41400, Batch No BP 899-597
Formulation: 1% Shampoo
Route: Dermal
Dose Levels: C, VC, 1, 10, 25 mg/kg/day
Strain: NZW
Number: 4/sex/dose level
Control Treatment: C received physiological saline, VC received placebo shampoo.

Study Site/Date: Janssen Pharmaceutica, Beerse, Belgium/April 87-Feb. 88
GLP/QAU Statement: Both present Vol. 1.5, p. 00-00144.

Ketoconazole 1% shampoo was applied to the clipped skin, either abraded or intact, for one hour each day for 28 days. The dosage levels were 0.1, 1, and 2.5 ml/kg. The study includes clinical signs, bodyweight, eye examinations, hematology, blood chemistry, urinalysis, organ weights, and gross pathology.

Results: One control animal died day 18. There were no dose-related clinical signs (one mid dose and one high dose animal developed crusts/purulent pustulae), changes in body weight, or adverse effects on hematology. LDH values decreased in the mid and high dose but were apparently within the historical range. Other blood chemistry parameters that were significant did not show a dose-relationship and were within historical limits. No drug related eye toxicity occurred. Urinalysis was normal. Relative and absolute heart weights decreases in high dose - gross lesions appeared to be randomly distributed.

Conclusion: The administration of the 1% shampoo at 1, 10, and 25 mg/kg for one hour each day for twenty-eight days to the abraded or intact skin of rabbits produced no adverse effects.

Rabbit: 7-Day Primary Dermal Irritation Study:

This study was conducted by Johnson and Johnson on ketoconazole 2% shampoo. The shampoo was applied (0.3 ml/test site) for 6 hours/day for 7 days under an occlusive patch to 6 NZW rabbits. A Draize Primary Dermal Irritation Index of 6.7 was obtained, classifying the 2% shampoo as a severe irritant. The sponsor indicates this is consistent with other marketed products, such as Head and Shoulders Shampoo.

Rabbit: 6-Month Dermal Toxicity Study: No. 1703

Compound: R 41400, Batch No. F0901
Formulation: 2% Shampoo
Route: Dermal
Dose Levels: 0, VC, 2, 20, 50 mg/kg/day, 1 hour contact
Strain: NZW
Number: 4/sex/dose
Control Treatment: 0 control received physiological saline
VC received shampoo without ketoconazole
Study Site/Date: Janssen Pharmaceutica, Beerse, Belgium/July 86-Nov. 87
GLP/QAU Statements: Both present, Vol. 1.4, p. 00-00002

The 2% shampoo was applied to the abraded and intact clipped skin one hour each day for six months. Dose levels were 0.1 ml (2 mg/kg), 1 ml (20 mg/kg), and 2.5 ml (50 mg/kg). The study includes clinical signs, body weight, hematology, blood chemistry, organ weights, and gross and histopathology (control and high dose). Body weight, hematology, blood chemistry, organ weights, and histopathology were analyzed by Mann-Whitney U Test.

Results: Sporadic skin lesions, diarrhea, and respiratory difficulties in all groups - slight skin erythema at times, mostly on intact ares - one VC animal died week 18 (pneumonia) - no drug related eye toxicity - no abnormal body weight changes - significant increases in week 13 RBC (low, mid, high) - significant increase in week 26 Hct (mid) and RBC (mid) - significant decrease in week 13 MCV (VC, low, mid, high) and MCH (mid) - significant decrease in week 26 MCV (VC, low, mid) and MCH (low, mid) - significant decrease in glucose (high), total bilirubin (mid), GGT (VC), and significant increase in LDH (low) - significant decrease in relative spleen weights (high) - no drug or dose related lesions on abraded or intact skin - slight increases in mean scores were reported for lesions in other tissues, but were not considered to be significant.

Discussion: The significant changes observed in some of the hematology and blood chemistry parameters appeared to fall within the normal range. Draize irritation scores indicated no dermal toxicity. No systemic toxicity effectgs were evident and no sensitization occurred. The 2% shampoo was well tolerated upto 2.5 ml/kg (50 mg/kg) for 6 months.

SPECIAL STUDIES:

Primary Ocular Irritation Study:

The ocular irritation potential of 0.3% and 2% ketoconazole shampoo was evaluated in NZW rabbits. The low dose was prepared by diluting the 2% solution with sterile water. Six rabbits/group received 0.1 ml solution/treated eye. The results are indicated in the following table.

Parameters	Undiluted 2% Shampoo	Diluted 0.3% Shampoo
	Number of Reacting Rabbits	Number of Reacting Rabbits
Cornea	6/6	0/6
Iris	1/6	0/6
Conjunctiva	5/6	0/6

The 2% shampoo was classified as a positive ocular irritant. The diluted sample was negative, producing only slight erythema and chemosis. The sponsor indicates these results are consistent with the results of experiments with marketed shampoos, i.e., Head and Shoulders.

A second studywas conducted with vehicle control, 1% and 0.15% ketoconazole shampoo, prepared by diluting the 1% shampoo with sterile water. The diluted shampoo was classified as a negative eye irritant. Both the vehicle control and the 1% shampoo were classified as positive ocular irritants.

Primary Dermal Irritation Study:

Dermal irritation was evaluated with a 1% and a 0.15% ketoconazole shampoo in NZW rabbits. The dose was 0.3 ml/test site with an occlusive patch. Erythema, escar, and edema formation were evaluated in twelve rabbits/group. The results are given below.

	0.15%	1%
Sum of Mean Scores	7.5	19.1
Primary Dermal Irritation Index	1.9	4.8
Classification	Mild Irritant	Moderate Irritant

ADME STUDIES:

Dermal absorption was evaluated in the 28-day rabbit dermal irritation study(Study No. 1683). Blood smaples were taken 2 hours after the last application on day 28. The animals were treated daily with 2, 20, and 50 mg/kg on intact and abraded skin. Plasma concentrations of ketoconazole were determined with HPLC. The detection limit was 5 ng/ml. Ketoconazole was not detected in any of the treated rabbits.

PACKAGE INSERT:

The pharmacologyand toxicology portion ofthe package insert and proposed labeling are accurate.

SUMMARY AND EVALUATION:

Nizoral (ketoconazole) 2% shampoo described in this NDA is for the relief of signs and symptoms associated with dandruff and seborrheic dermatitis. The shampoo is to be used twice a week for four weeks with at least three days between each shampooing.

Janssen has two other approved NDAs: Nizoral Tablets (NDA 18-533) for the treatment of systemic fungal infections (in HFD-530) and Nizoral 2% Cream (NDA 19-084) for topical treatment of tinea corporis, tinea cruris, and tinea versicolor.

In the 28-day rabbit dermal studies (2, 20, 50 mg/kg), plasma levels of ketoconazole could not be detected when measured two hours after the last dose using HPLC with a detection limit of 5 ng/ml. In earlier studies the half-life of ketoconazole was found to be 1.75 hours. It is not surprising that systemic toxicity was not observed in these studies or in the 6 month dermal toxicity study in rabbits. The 2% shampoo produced dermal irritation and can be classified as a positive ocular irritant.

The acute oral toxicity of the 2% shampoo in rats produced diarrhea , decreased activity, and sensitivity to touch. The dose producing lethality in half the animals was 15 ml/kg (300 mg/kg) in the mouse and 10 ml/kg (200 mg/kg) in the rat.

An eighteen-month carcinogenicity feeding study in mice (5, 20, 80 mg/kg/day) and a two year carcinogenicity feeding study in rats (5, 20, 80 mg/kg/day) were completed for NDA 18-533. There was no evidence of oncogenic activity in either study. The Ames assay, the dominant lethal test, and a micronucleus test also gave negative results.

Ketoconazole has been shown to be teratogenic (syndactylia and oligodactylia) in the rat when administered at 80 mg/kg/day in the diet.

The proposed labeling adequately reflects the pharmacology and toxicology of ketaconazole.

RECOMMENDATIONS:

I recommend approval of this submission.

Almon W. Coulter

Almon W. Coulter, Ph.D.

cc: Orig. NDA 19-927
HFD-340
HFD-502/JWeissinger
HFD-520
HFD-520/Pharm/Coulter
HFD-520/MO/Huene
HFD-520/CSO/Bostwick
HFD-520/Coulter/kjs/2/17/89
R/d init.by:JMDavitt 2/22/89
1202p