CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-310

MICROBIOLOGY REVIEW(S)

Division of Anti-Infective Drug Products (HFD-520)
Microbiology and Drug Control Review Notes #1

NDA # 20-310 DATE COMPLETED: May 6, 1993

APPLICANT:

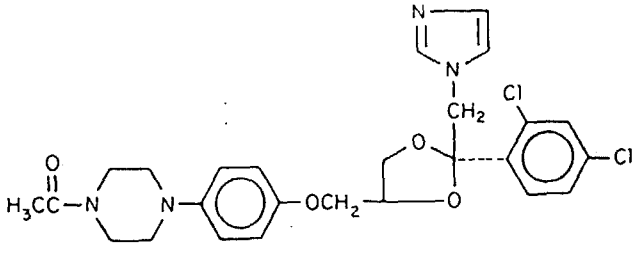
Johnson & Johnson Consumer Products, Inc.
Grandview Road
Skillman, NJ 08558-9418

CHEM/THER. TYPE:

SUBMISSION REVIEWED:
PROVIDING FOR: Controls the flaking, scaling and itching associated with dandruff

PRODUCT NAMES(S):
Proprietary: To be named
Non-Proprietary/USAN: Ketoconazole (USP)
Code Name or Number:
Chemical: Piperazine, l-acetyl-4-((2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl)methoxy)phenyl-,cis-

STRUCTURAL FORMULA:



Empirical Formula $C_{26}H_{28}Cl_2N_4O_4$
MOL. WT. = 531.44

DOSAGE FORMS(S) and STRENGHTS: Shampoo (emulsion) 1%

ROUTE(S) OF ADMINISTRATION: Topical

PHARMACOLOGICAL CATEGORY: Antifungal

INITIAL SUBMISSION:
Received by CDER:
Received by Reviewer: Received desk copy Vol. 1.1 Dated Dec 18,1992
Review Completed:

REMARK(S):

Microbiology review was initiated at the request of the reviewing chemist Dr.Tso. Cursory review of the application indicated that the formulation contains a preservative, however no data was provided to establish effectiveness of the preservative used.

On April 1, 1993 via telephone the applicant was informed by Ms Cook about the microbiology deficiencies, and the applicant was asked to submit the relevant data to support effectiveness of the preservative used in the formulation.

On May 3, 1993 the applicant has replied to Ms.Cook's request and submitted the test data. This review entails evaluation of the data submitted by the applicant.

CONCLUSIONS and/or RECOMMENDATIONS:

Stability samples from one batch (#899-1374) of the drug product were tested for effectiveness. The preservative efficacy test data provided by the applicant clearly shows that the product meets the criteria for the product to be considered adequately preserved.

Considering the available data in support of the microbiological stability, I recommend approval of the NDA.

I recommend further that the samples from 3 batches of the intended marketed drug product be placed on stability, tested for effectiveness of the preservative and to report the results in the future annual reports.

Pandu R. Soprey, Ph.D.
Microbiologist, HFD-520

cc: Orig. NDA # 20-310
HFD-473
HFD-635
HFD-502
HFD-520
HFD-520/Micro/Soprey
HFD-520/Chem/Tso
HFD-520/MO/Labib
This review contains 5 pages

HFD-520/DDir/Gavrilovich
HFD-520/SMicro/Sheldon
RD Init 5-11-93 5/11/93

HFD-520/Pharm/Joshi
HFD-520/CSO/Cook

Microbiological Review:

The drug product presented in this NDA is a aqueous based shampoo containing 1% ketoconazole (formula 1760-156). The drug product contains the preservative ... and a preservative potentiator, tetrasodium EDTA.

The product has been reported as adequately preserved as referenced in the NDA, Volume 1.3 pages 006-118 and in the 4-month safety update pages 184-203.

The preservative effectiveness of the drug product is based on the results of USP <51> Antimicrobial Preservative Effectiveness test and the Johnson & Johnson Consumer Products Test Methods 7907 (42-day multi-challenge) and 7965 (28-day single challenge). The Johnson & Johnson Test Methods 7907 and 7965 incorporates the test microorganisms stipulated in the USP, plus additional cultures isolated from manufacturing environments and deionized water. The list of test cultures used and the protocols to perform the modified preservative effectiveness test are provided. The protocols are satisfactory to evaluate the drug product.

Effectiveness of the preservative was evaluated by testing the stability samples from one batch (899-1374) the drug product The test data showing susceptibility of the bacterial, and the fungal cultures is provided in this submission.

The product is considered adequately preserved if each inoculum type (bacteria and fungi) is reduced by 3 logs within seven days (of each inoculation) with further reduction in count to 4 logs within 14 days of the last inoculation and no increase in count for the duration of the test. Total count results for each microbiological evaluation within each efficacy challenge test are provided and results indicate that the product is adequately preserved.

The test results are summarized in the table below.

SUMMARY OF PRESERVATIVE EFFECTIVENESS TEST

Sample	Stability Period	Length of Test	Test Results[1]
JJ-62	Fresh	28 days	Pass
		42 days	Pass
JJ-66	4 week	28 days	Pass
JJ-67	4 week	28 days	Pass
JJ-104	13 week	28 days	Pass
JJ-175	26 week	28 days	Pass
JJ-322	1 year	28 days	Pass
JJ-564	2 year	28 days	Pass

[1] -Based on the reduction of the test microorganisms to the level as specified in the test specifications.

Microbial Limits Test USP is to be performed on the finished dosage form as a regulatory test and test requirements are; " the drug product shall contain no detectable harmful microorganisms and the total microbial count shall not be >10 CFU/g of product".

MAR 14 1994

Division of Anti-Infective Drug Products (HFD-520)
Microbiology and Drug Control Review #2

NDA # 20-310 **DATE COMPLETED: March 8, 1994**

APPLICANT:

Johnson & Johnson Consumer Products, Inc.
Grandview Road
Skillman, NJ 08558-9418

CHEM/THER. TYPE:

SUBMISSION REVIEWED: General Correspondence Labeling
PROVIDING FOR: Changes in the labeling

PRODUCT NAMES(S):
Proprietary:
Non-Proprietary/USAN: Ketoconazole (USP)
Code Name or Number:
Chemical: Piperazine, l-acetyl-4-((2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl)methoxy)phenyl-,cis-

STRUCTURAL FORMULA:

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ROUTE(S) OF ADMINISTRATION: Topical

PHARMACOLOGICAL CATEGORY: Antifungal

INITIAL SUBMISSION:
Received by CDER: 28-02-94
Received by Reviewer: 08-03-1994

REMARK(S):

The proposed container labeling presented in the submission follow the recommendation made by the Dermatologic Drugs Advisory Committee and Nonprescription Drug Advisory Committee Meeting held on 16 February, 1994.

Microbiology issues pertaining to this NDA were reviewed in Microbiology Review of 6-May-1993 and it was recommended that the NDA should be approved.

CONCLUSIONS and/or RECOMMENDATIONS:

No microbiology issues are pending and I recommend approval of the proposed label

Pandu R. Soprey, Ph.D.
Microbiologist, HFD-520

cc: Orig. NDA # 20-310
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HFD-520
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3/14/94