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RESEARCH**

APPLICATION NUMBER:

21-738

MICROBIOLOGY REVIEW

NDA 21738
Ketoconazole Foam 2%
Connetics Corporation

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**DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS (HFD-520)
MICROBIOLOGY REVIEW CONSULT FOR HFD-540
REVIEW #1**

NDA #21 738

Date Review Completed: March 12, 2004

Applicant (NDA):

Connetics Corporation
3290 West Bayshore Road,
Palo Alto, CA 94303

Contact Person:

Eleanor V. Chiu
Director, Regulatory Affairs
650-843-2860

Chem/Ther. Type: Ketoconazole 2% foam

Submissions Reviewed: Draft label package insert for NDA 21 738, Microbiology Consult for HFD 540

Providing for: Topical treatment of seborrheic dermatitis

Product Name(s):

Proprietary: Extina™ (ketoconazole) 2% foam

Non-proprietary/USAN: N/A

Compendia: N/A

Code name/number: Extina™

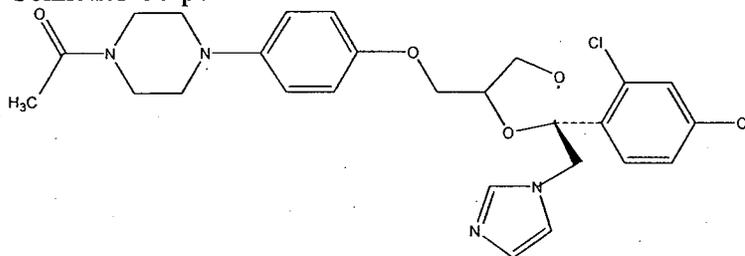
Chemical name:

Ketoconazole is Piperazine, 1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-,cis-

Structural formula:

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Ketoconazole Foam 2%
Connetics Corporation

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Dosage form(s): Foam

Route(s) of administration: Topical, dermal only

Pharmacological Category: Antifungal (Azole)

Dispensed: Rx X OTC

Initial Submission Dates

Received by CDER: 27 February 2004
Received by Reviewer: 27 February 2004
Review Completed: 11 March 2004

Supplements/Amendments: N/A

Related Documents: NDA 21 738

Purpose of Submission:

Connetics Corporation submitted an original NDA for Ketoconazole Foam, 2% for the topical treatment of seborrheic dermatitis under the FD&C Act, Section 505(b)(2) and 21 CFR Part 314. In a letter to the Agency dated January 23, 2004, the applicant provides to the Division of Dermatologic and Dental Drug Products (HFD-540) a revised draft labeling package insert. Microbiology is consulted to assess the Microbiology section of the proposed draft label. No microbiology volumes are submitted with the NDA.

General Information:

Seborrheic dermatitis occurs most commonly on lipid-rich areas of the skin, especially the face, chest, and scalp. The role of *Malassezia* in this disease remains controversial¹. Most of the evidence for the relationship, however, comes from the efficacy of antifungal drugs. Improvement in the disease is paralleled by a reduction in the number of *Malassezia* species, while recolonization results in disease recurrence.

For the purpose of reference only, the microbiology reviewer studied labels of other products containing 2% ketoconazole for which treatment of seborrheic dermatitis is

Ketoconazole Foam 2%

Connetics Corporation

indicated. The reviewer found that in at least 2 products, Nizoral[®] 2% Cream² and Nizoral[®] 2% Shampoo³ the microbiology section includes reference to potential association between certain fungi and the disease indication. Specifically, the label for Nizoral[®] 2% Cream includes the following statement:

b(4)

Comments:

A relationship between the antifungal activity against a given pathogen and any observed clinical benefit cannot be established without the drug showing activity both in vitro and in clinical infections against the specific pathogen(s) involved. Review of the submissions shows that no microbiological assessment were included during the clinical studies and that no microbiological end points were included or claimed.

In the draft label provided by the applicant for Extina[™], the microbiology section includes a reference to information which is based on *in vitro* inhibitory activity of ketoconazole against several fungi. Page 2 of the draft label includes the following:

b(4)

The last sentence precisely states that fact _____ . However, the draft label includes the following statement on P. 2 under the Mode of Action:

b(4)

The statement seems to imply that the therapeutic effect is due to reduction of a specific pathogen. The sponsor is advised that this statement should be changed to reflect the fact that there was no microbiological assessment during clinical studies. It is further emphasized that the use of the word '_____' implies that quantitative or semi-quantitative microbiological assessment was conducted, which is not the case.

Recommendations: to be communicated to sponsor

Based on the above information, the microbiology reviewer recommends that the statement _____ be deleted.

b(5) b(4)

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Ribhi Shawar, Ph.D., ABMM
Microbiologist, HFD-520
4 March 2004

Lea Carrington
HDF-540
cc: NDA 21 738

Concurrence: **RD#1 Initialed 03/11/04, Final 03/12/04 ATS**
HFD-520/TLMicro/A.T. Sheldon

HFD-520/Dept/Dir/L. Gavrilovich

HFD-520/DepDir/LGavrilovich
HFD-520/Smicro/ATSheldon
HFD-520/Micro
HFD-540/CSO/L Carrington

REFERENCES:

¹ Gupta et al., Superficial fungal infections: an update on pityriasis versicolor, seborrheic dermatitis, tinea capitis, and onychomycosis. 2003. Clinics in Dermatology. 21: 417-425

² Nizoral[®] Cream Package Insert

³ Nizoral[®] Shampoo Package Insert.

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/s/

Ribhi Shawar
3/12/04 08:47:33 AM
MICROBIOLOGIST

Albert Sheldon
3/12/04 09:38:48 AM
MICROBIOLOGIST
PM: Please note comment to applicant.

Albert Sheldon
3/12/04 09:41:22 AM
MICROBIOLOGIST
PM: Please note comment to applicant.

Lillian Gavrilovich
3/12/04 03:38:26 PM
MEDICAL OFFICER

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