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RESEARCH**

*APPLICATION NUMBER:*

**21-738**

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

## Clinical Pharmacology Review

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PRODUCT (Generic Name):	Ketoconazole (2%) Foam
PRODUCT (Proposed Brand Name):	Extina Foam
DOSAGE FORM:	Topical Foam
DOSAGE STRENGTH:	2% Foam
NDA:	21-738 (Resubmission of Original NDA)
PROPOSED INDICATIONS:	Seborrheic Dermatitis
NDA TYPE:	505(b)(2)
SUBMISSION DATE:	December 11, 2006
SPONSOR:	Connectics
REVIEWER:	Tapash K. Ghosh, Ph.D.
TEAM LEADER:	Sue Chih Lee, Ph.D.
OCP DIVISION:	DCP III,
OND DIVISION:	HFD 540

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### EXECUTIVE SUMMARY

Ketoconazole is a broad-spectrum synthetic imidazole antifungal agent currently being used both orally and topically. The sponsor originally submitted for approval this new dosage form (2% Topical Foam of Ketoconazole) for the topical treatment of \_\_\_\_\_ Seborrheic Dermatitis on January 23, 2004 and received the Agency's Not Approvable letter dated November 23, 2004. The clinical pharmacology and biopharmaceutics review of the original NDA 21-738 consists of 1 pivotal study to evaluate the comparative bioavailability of Ketoconazole Foam, 2%, versus Nizoral® (ketoconazole) 2% Cream in subjects with moderate to severe Seborrheic Dermatitis. Overall, absorption of ketoconazole in subjects treated with Ketoconazole Foam was higher than in subjects treated with Nizoral Cream; however, these levels of ketoconazole are significantly lower than levels observed following oral administration of ketoconazole. The Clinical Pharmacology and Biopharmaceutics section of the original NDA 21-738 was acceptable.

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However, the original submission (NDA21-738) received the Agency's "Not Approvable" letter dated November 23, 2004 stating the following deficiencies:

The data from study KFD.C.002 do not support the conclusion that ketoconazole foam, 2%, is effective for the treatment of seborrheic dermatitis. Study KFD.C.002 was designed to evaluate whether ketoconazole foam was superior to its vehicle and non-inferior to the active comparator. However, the superiority was not demonstrated for the primary efficacy parameter that was defined prospectively. Because this deficiency cannot be addressed with additional analyses of study KFD.C.002, results from one additional adequate and well-controlled study will need to be submitted demonstrating superiority of ketoconazole foam, 2%, over its vehicle and non-inferiority to the active comparator.

The subject of this application is the sponsor's response to the NA letter. The sponsor submitted class 2 resubmission to the unapproved NDA addressing deficiencies cited by the Agency with the inclusion of a second Phase 3 study in which, according to the sponsor, the superiority of ketoconazole foam to vehicle foam, and the non-inferiority of ketoconazole foam to its reference listed comparator, have been unambiguously established. As no deficiency in the area of clinical pharmacology was cited in the "NA" letter, the sponsor did not submit any new information that requires clinical pharmacology review.

**Recommendation:**

No action is necessary for the clinical pharmacology aspect of this amendment.

Primary Reviewer:

Tapash K. Ghosh, Ph.D.  
Clinical Pharmacology  
Division of Clinical Pharmacology III

Team Leader: Sue Chih Lee, Ph.D. \_\_\_\_\_

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## Clinical Pharmacology/Biopharmaceutics Review

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PRODUCT (Generic Name):	Ketoconazole (2%) Foam
PRODUCT (Proposed Brand Name):	Extina Foam
DOSAGE FORM:	Topical Foam
DOSAGE STRENGTH:	2% Foam
NDA:	21-738
PROPOSED INDICATIONS:	Seborrheic Dermatitis
NDA TYPE:	505(b)(2)
SUBMISSION DATE:	January 26, 2004
SPONSOR:	Connectics
REVIEWER:	Tapash K. Ghosh, Ph.D.
Acting TEAM LEADER:	Raman Baweja, Ph.D.
OCPB DIVISION:	DPE III, HFD 880
OND DIVISION:	HFD 540

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### EXECUTIVE SUMMARY

Ketoconazole is a broad-spectrum synthetic imidazole antifungal agent currently being used both orally and topically. The sponsor submitted for approval this new dosage form (2% Topical Foam of Ketoconazole) for the topical treatment of \_\_\_\_\_ Seborrheic Dermatitis. The clinical pharmacology and biopharmaceutics review of this NDA 21-738 consists of 1 pivotal study to evaluate the comparative bioavailability of Ketoconazole Foam, 2%, versus Nizoral<sup>®</sup> (ketoconazole) 2% Cream in subjects with moderate to severe Seborrheic Dermatitis. Overall, absorption of ketoconazole in subjects treated with Ketoconazole Foam was higher than in subjects treated with Nizoral Cream; however, these levels of ketoconazole are significantly lower than levels observed following oral administration of ketoconazole.

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The summary of the DRAFT clinical review for study KFD.C.002 as of 9/9/2004) is as follows:

Ketoconazole Foam was non-inferior to Nizoral Cream, but Ketoconazole Foam was not superior to its vehicle. Because it is necessary for a demonstration of effectiveness that the product is shown to be superior to its vehicle, the clinical reviewer concludes that the effectiveness of the foam has not been established. Therefore, the clinical reviewer recommends that this application is not approvable for Ketoconazole Foam 2% for the indication of the topical treatment of seborrheic dermatitis. The clinical reviewer lists the following for approval:

1. A controlled clinical trial which compares Ketoconazole Foam to the foam vehicle, with results that show that the active foam is superior to its vehicle.
2. An additional sensitization study.
3. A 21 day cumulative irritation study.
4. A long term open label safety study.

**Recommendation:**

The Clinical Pharmacology and Biopharmaceutics section of NDA 21-738 is acceptable with the suggested labeling changes as described below.

**CPB Labeling:** The following section describes the sponsor's proposed labeling with suggested changes from CPB perspective. ABC indicates suggested inclusion.

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Primary Reviewer:

Tapash K. Ghosh, Ph.D.  
Clinical Pharmacology and Biopharmaceutics  
Division of Pharmaceutical Evaluation III

Team Leader: Raman (Ray) Baweja, Ph.D. \_\_\_\_\_

## BACKGROUND

Ketoconazole, a broad-spectrum synthetic imidazole antifungal agent, is used both orally and topically. Its oral and 2% topical formulations were approved in 1981 and 1985, respectively, and 2% shampoo for dandruff was approved in 1990. In addition, a generic topical cream was cleared for marketing in 2000, and 1% over-the-counter shampoo for dandruff was approved in 1997. Janssen Pharmaceutical markets these products under the trade name Nizoral®. Topically, the drug has been used to treat seborrheic dermatitis, tinea corporis, tinea cruris, tinea pedis, tinea versicolor, and cutaneous candidiasis. The proposed topical formulation Extina™ (Ketoconazole Foam, 2%) submitted under section 505 (b) (2) is aimed to treat seborrheic dermatitis.

## GENERAL ATTRIBUTES

**Trade name:** Extina™ (Ketoconazole Foam, 2%)

**Generic name:** Ketoconazole

**Chemical name:** \_\_\_\_\_

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**Molecular formula/molecular weight:** C<sub>26</sub>H<sub>28</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>4</sub>/531.43

**Chemical Structure:**

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## Formulation:

<u>Component<sup>a</sup></u>	<u>Function</u>	<u>Percent(w/w)<sup>b</sup></u>
Ketoconazole, USP	Active ingredient	2.00
<u>Excipients</u>		
Cetyl alcohol, NF	┌	└
Denatured alcohol	┌	└
Citric acid, USP		
Polysorbate 60, NF		
Potassium citrate, USP		
Propylene glycol, USP		
Purified water, USP		
Stearyl alcohol, NF	└	└

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<sup>a</sup> \_\_\_\_\_  
<sup>b</sup> Concentration/can

**Overview of Clinical Studies:** The following clinical trials have been submitted in support of the application.

Study #	Design	# pts
KFD.C.004	Contact Sensitization	192
KFD.C.003	Comparative BA	21
KFD.C.002	Phase 3 safety and efficacy	619

**Clinical Pharmacology and Biopharmaceutics:** The clinical pharmacology and biopharmaceutics review of this NDA 21-738 consists of 1 pivotal study to evaluate the comparative bioavailability of Ketoconazole Foam, 2%, versus Nizoral® (ketoconazole) 2% Cream in subjects with moderate to severe Seborrheic Dermatitis. Nizoral Cream was chosen as the comparator product for this study because it is the only topically administered ketoconazole 2% that is currently marketed for the treatment of seborrheic dermatitis. Furthermore, Nizoral Cream has been identified as the referenced listed drug for the development of Ketoconazole Foam in a 505(b)(2) application route.

Overall, absorption of ketoconazole in subjects treated with Ketoconazole Foam was higher than in subjects treated with Nizoral Cream. There appeared to be no correlation between amounts of study drug applied, extent of seborrheic dermatitis, or severity of disease and absorption of ketoconazole. The resulting increased absorption of the foam product as compared to the cream may be due to differences in the vehicle.

**Efficacy:** Study KFD.C.002 (reviewed by the clinical reviewer) has been submitted as the pivotal study for a demonstration of safety and efficacy. This was a double blind, multicenter, randomized comparison of Ketoconazole Foam 2% with Nizoral (ketoconazole) Cream 2%, and with the cream and foam vehicles, in the treatment of patients with mild to severe seborrheic dermatitis. Applications were made twice daily for four weeks. The pertinent efficacy parameters were scoring of erythema and scaling at a target lesion, and an Investigator's Static Global Assessment (ISGA). The predesignated primary efficacy variable was the proportion of patients with an ISGA score of 1 or 0 at the end of treatment. The clinical reviewer's draft review as of 9/9/2004 mentions that Ketoconazole Foam was noninferior to Nizoral Cream, but that Ketoconazole Foam was not superior to its vehicle. Further, because it is necessary for a demonstration of effectiveness that the product is shown to be superior to its vehicle, the conclusion is that the effectiveness of the foam has not been established.

**Safety:** Adverse events in Study 002 were local cutaneous burning, stinging, itching, or tingling in approximately 15% of patients with both Ketoconazole Foam and its vehicle. Laboratory tests, including hemograms and clinical chemistries, showed no drug-related changes.

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NDA: 21-738/Study KFD.C.003

Study Dates: Dec '02 – Feb '03

**A Randomized, Open Label Study to Evaluate the Comparative Bioavailability of Ketoconazole Foam, 2%, versus Nizoral® (ketoconazole) 2% Cream in Subjects with Moderate to Severe Seborrheic Dermatitis**

**Objective:** The objective of this study was to evaluate the comparative bioavailability of Ketoconazole Foam, 2% (Ketoconazole Foam) versus Nizoral® (ketoconazole) 2% Cream (Nizoral Cream) in the treatment of seborrheic dermatitis.

**Overall Study Design:** This was a multicenter (2 centers), randomized, open-label study to evaluate the comparative bioavailability of Ketoconazole Foam versus Nizoral® Cream in 24 subjects with moderate to severe seborrheic dermatitis with an Investigator's Static Global Assessment score of 3 or 4 at Baseline. The subjects were enrolled and randomly assigned to 1 of 2 parallel treatment groups in a 1:1 ratio of Ketoconazole Foam or Nizoral Cream.

A serum sample was collected, prior to first application of study drug, for baseline bioavailability evaluation. Subjects self administered 3 grams of the treatment (Ketoconazole Foam or Nizoral Cream) twice daily with a minimum of 8 hours between applications for 4 weeks. At Visit 2 (Week 2/Day 15) and Visit 3 (Week 4/Day 29 or Early Termination) subjects were queried for concomitant medication use, adverse experiences and compliance with the study treatment regimen; and serum samples for bioavailability were collected between 30 minutes and 12 hours following application of study drug. Concentrations of ketoconazole in serum samples were analyzed by \_\_\_\_\_ using an LC/MS/MS validated assay with a limit of quantitation of 2.00 ng/mL. For ketoconazole levels reported as below the limit of quantitation (BLQ) of the assay, the value 0.0 was assigned for calculation and description purposes.

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**Results:** For each treatment group, the mean, median, standard deviation and range of ketoconazole blood levels were calculated for each visit, and are presented in Table 1 and individual ketoconazole blood levels are presented in Table 2 below:

**Table 1: Summary of Ketoconazole Blood Levels (ng/mL)**

	Ketoconazole Foam	Nizoral Cream
<b>Number of Subjects</b>	12	12
<b>Baseline</b>		
n	12	12
mean (SD)	0.2 (0.771)	0.0 (0.000)
median	<2.00	<2.00
min, max	(<2.00, 2.67)	(<2.00, <2.00)
<b>Week 2</b>		
n	12	10
mean (SD)	4.2 (2.569)	0.6 (1.279)
median	3.2	<2.00
min, max	(2.32, 11.10)	(<2.00, 3.74)
<b>Week 4/End of Treatment</b>		
n	12	9
mean (SD)	5.1 (2.332)	1.5 (1.565)
median	4.9	2.0
min, max	(2.45, 10.90)	(<2.00, 4.25)

**Table 2: Individual Ketoconazole Blood Levels (ng/mL)**

<b>Ketokonazole Foam</b>							
Site-Sub	Total Extent of Seb Derm (%)	ISGA Score	Visit				
			Baseline	# 2		#3	
				Interval	Concn. (ng/ml)	Interval	Concn (ng/ml)
101-001	1	3	BLQ	1h 12 min	2.99	4 h 23 min	5.55
101-003	2	3	BLQ	35 min	4.03	5 h 48 min	4.03
101-005	3	3	BLQ	36 min	3.42	40 min	4.34
101-007	5	3	BLQ	1 h 21 min	5.16	2h 20 min	7.22
101-016	2	4	2.67	4 h 25 min	2.96	1 h 03 min	2.85
101-018	15	4	BLQ	6 h 38 min	2.32	2h 54 min	2.45
102-009	1	3	BLQ	4 h 30 min	2.80	2 h 15 min	3.11
102-012	2	3	BLQ	2 h 00 min	11.1	50 min	5.52
102-112	2	3	BLQ	3 h 28 min	7.31	2 h 35 min	10.9
102-119	2	3	BLQ	9 h 20 min	2.92	5 h 46 min	5.67
102-022	1	3	BLQ	4 h 50 min	3.58	2 h 40 min	3.47
102-024	1	3	BLQ	4h 59 min	2.40	1 h 50 min	5.86
Mean	3.08	3.17			4.25		5.08
SD	3.92	0.39			2.57		2.33
Median	2.00	3.00			3.21		4.93
Max	15	4			11.1		10.9
Min	1	3			2.32		2.45
<b>Nizoral Cream</b>							
101-002	1	3	BLQ	X	X	X	X
101-004	4	3	BLQ	31 min	BLQ	3 h 13 min	BLQ
101-006	5	3	BLQ	3 h 10 min	3.74	1 h 47 min	2.86
101-008	2	3	BLQ	1 h 53 min	BLQ	3 h 06 min	BLQ
101-015	15	3	BLQ	10 h 54 min	BLQ	10 h 18 min	4.25
101-017	5	3	BLQ	X	X	X	X
102-010	1	3	BLQ	8 h 25 min	BLQ	8 h 20 min	BLQ
102-011	1	3	BLQ	1 h 00 min	BLQ	59 min	BLQ
102-014	2	3	BLQ	9 h 25 min	BLQ	9 h 38 min	2.20
102-020	1	3	BLQ	35 min	BLQ	2 h 55 min	2.16
102-021	2	3	BLQ	1 h 31 min	BLQ	1 h 15 min	2.00
102-023	1	3	BLQ	39 min	2.01	X	X
Mean	3.33	3	NA		0.60		1.50
SD	3.98	0	NA		1.28		1.57
Median	2	3	NA		<2.0		2.0
Max	15	3	NA		3.74		4.25
Min	1	3	NA		<2.0		<2.0

\*Interval between Drug administration and blood sample collection time. The value 0.0 was assigned for calculation for BLQs.

All subjects except one in the Ketoconazole Foam treatment group (Subject No. 101-016) had Baseline levels of ketoconazole that were below the limit of quantitation (BLQ). Subject No. 101-016 had a Baseline ketoconazole level of 2.67 ng/mL. This subject used both Nizoral Shampoo and Nizoral 2% Cream for treatment of seborrheic dermatitis for approximately 6 years and had discontinued use of these medications 15 days prior to enrollment in this study.

All subjects enrolled in this study had an Investigator's Static Global Assessment Score of 3 at Baseline, except for 2 subjects enrolled in the Ketoconazole Foam treatment group (Subject Nos. 101-016 and 101-018) who each had a score of 4 at Baseline. These 2 subjects with more severe seborrheic dermatitis at baseline did not have higher levels of ketoconazole at post-Baseline visits; all blood levels for these subjects were < 3 ng/mL. Therefore, based on limited available data, there appeared to be no correlation between extent of seborrheic dermatitis (% BSA affected) or severity of disease and absorption of ketoconazole.

A summary of ketoconazole levels collected at various time points following application of study drug is shown in Table 3.

**Table 3: Summary of Ketoconazole Blood Levels (ng/ml) by Time Post-Application**

	<b>Ketoconazole Foam<sup>a</sup></b>	<b>Nizoral Cream</b>
<b>Total Number of Samples Collected</b>	23	19
<b>30 minutes –&lt;3 hours Post-Application</b>		
n	13	10
mean (SD)	5.4 (2.807)	0.9 (1.189)
median	4.3	<2.00
min, max	(2.85, 11.10)	(<2.00, 2.86)
<b>3 hours –&lt;6 hours Post-Application</b>		
n	8	3
mean (SD)	4.3 (1.722)	1.2 (2.159)
median	3.8	<2.00
min, max	(2.40, 7.31)	(<2.00, 3.74)
<b>6 hours –&lt;12 hours Post-Application</b>		
n	2	6
mean (SD)	2.6 (0.424)	1.1 (1.787)
median	2.6	<2.00
min, max	(2.32, 2.92)	(<2.00, 4.25)

<sup>a</sup> Visit 3 sample results for Subject No. 101-018 not included, collected > 12 hours following application of study drug

For the Ketoconazole Foam treatment group, blood levels of ketoconazole were highest within the time period of 30 minutes to 3 hours following application of study drug and tended to decrease in the time periods of 3–6 hours and 6–12 hours following study drug application. This is expected as the PK profile following oral administration

demonstrates that plasma elimination of ketoconazole is biphasic with a half-life of 2 hours during the first 10 hours and 8 hours thereafter. Due to overall low levels of ketoconazole in the Nizoral Cream treatment group, analysis of blood levels with respect to time following study drug application is difficult.

### **Conclusions**

Overall, absorption of ketoconazole in subjects treated with Ketoconazole Foam was higher than in subjects treated with Nizoral Cream. Detailed PK analysis and estimation of PK parameters were not performed for this study following application of Ketoconazole Foam as only a single blood sample was collected from subjects at study visit. There appeared to be no correlation between amounts of study drug applied, extent of seborrheic dermatitis, or severity of disease and absorption of ketoconazole. The resulting increased absorption of the foam product as compared to the cream may be due to differences in the vehicle. Ketoconazole levels from Extina foam are significantly lower than levels measured following oral administration of ketoconazole. Oral administration of ketoconazole results in blood concentrations of ketoconazole of 3.5  $\mu\text{g/mL}$  (or 3500  $\text{ng/mL}$ ) within 1 to 2 hours following a single 200 mg dose (Nizoral Tablets PI, 1998). Mean trough concentrations of ketoconazole achieved with multiple oral doses of 400, 800 and 1200 mg/day were 3.21, 4.42 and 6.38  $\mu\text{g/mL}$ , respectively. These levels are approximately 300 to 600 fold higher than the maximum level attained with topical administration of Ketoconazole Foam.

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