

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-026**

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

## Clinical Pharmacology Review

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<b>NDA #</b>	21-026
<b>Submission Date (s)</b>	August 28 <sup>th</sup> , 2007
<b>Brand Name</b>	Vusion <sup>TM</sup> Ointment
<b>Generic Name</b>	0.25 % miconazole nitrate, 15 % zinc oxide and 81.35 % white petrolatum ointment
<b>Reviewer</b>	Abimbola Adebowale, Ph.D.
<b>Team Leader</b>	Lydia Velazquez, Pharm.D.
<b>OCP Division</b>	DCP-3
<b>OND Division</b>	Division of Dermal and Dental Products
<b>Applicant</b>	Barrier Therapeutics, Inc. Princeton, NJ 08540
<b>Submission Type</b>	Final Post-Marketing Study Report for a PK study
<b>Related IND #</b>	21,542
<b>Indication</b>	VUSION Ointment is indicated for the adjunctive treatment of diaper dermatitis only when complicated by candidiasis, in immunocompetent pediatric patients 4 weeks and older.

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#### 1. Executive Summary:

This supplement consists of a final study report of a pharmacokinetic study (PK) to fulfill the requirements of a Phase IV commitment that was included in the approval letter for Vusion ointment. Vusion ointment was approved on February 16<sup>th</sup>, 2006 for the adjunctive treatment of diaper dermatitis only when complicated by candidiasis, in immunocompetent pediatric patients 4 weeks and older.

The approval letter defined a (PK) post-marketing commitment (PMC) as follows:

*An open label study to assess the systemic absorption and safety of the marketed formulation of topically applied 0.25% miconazole nitrate, 15% zinc oxide, and*

***81.35% white petrolatum ointment in infants with moderate to severe diaper dermatitis when complicated by candidiasis.***

***Protocol Submission: by April 30, 2006***

***Study Start: by August 30, 2006***

***Final Report Submission: by August 30, 2007***

Therefore, in fulfillment of the PMC, this supplement contains a clinical study report entitled "An Open label Study to Assess the Systemic Absorption and Safety of Topically Applied 0.25 % Miconazole-Nitrate Ointment in Infants with Moderate to Severe Diaper Dermatitis" (Study Number BT0100-201-INT).

### **1.1 Recommendation:**

From a clinical pharmacology and biopharmaceutics perspective, the applicant has adequately fulfilled the requirements for the post marketing commitment for a Phase 4 study and their application is acceptable. Please refer to Section 3 on page 4 for our labeling recommendations.

### **1.2 Phase IV Commitments: Not Applicable**

### **1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings:**

The results of the final study report for protocol BT0100-201-INT that evaluated the plasma concentrations of miconazole in infants (n=17) aged 1-21 months old (who were hospitalized or in a controlled clinical setting), with moderate to severe diaper dermatitis, after multiple topical applications (5-12 times per day) of Vusion ointment for 7 days demonstrated that quantifiable (> LOQ of 0.5 ng/mL) plasma concentrations of miconazole was observed in about 12% of study patients (2/17 subjects). Two subjects had miconazole plasma concentrations values of 0.574 ng/mL and 0.581 ng/mL, respectively. The total amount of drug used by these two subjects was 42.7 g and 46.7 g respectively, which was in the lower range of the total amount of drug used (32g-78g) in the study.

A correlation between the observed systemic exposure, age of the patient, gender of patient, the severity of disease, or the amount of medication used was not observed. However, the number of patients (N=2) with quantifiable plasma concentrations limits any definitive conclusions from this data.

It is recommended that the results of this study be included in the clinical pharmacology section of the label.

This study report fulfils the requirement of the Phase IV commitment that was requested in the approval letter for Vusion.

**Signatures**

Primary Reviewer:

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Abimbola Adebawale, Ph.D.  
Clinical Pharmacology Reviewer  
Division of Clinical Pharmacology 3  
Office of Clinical Pharmacology

Team Leader Concurrence:

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Lydia Velazquez, Pharm.D.  
Team Leader  
Division of Clinical Pharmacology 3  
Office of Clinical Pharmacology

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## 2. QBR

### *What is the systemic exposure miconazole from the marketed formulation of Vusion in infants with moderate to severe diaper dermatitis?*

The results of study BT0100-201-INT indicated that quantifiable ( $>$  LOQ of 0.5 ng/mL) plasma concentrations of miconazole were observed in 12% of study subjects (2/17 subjects) following application (5-12 times per day) of the marketed formulation of Vusion. Fifteen of the 17 subjects had plasma concentrations of miconazole that were below the limit of quantitation (0.5 ng/mL). Two subjects (Subject 01-06 and Subject 01-17) had miconazole plasma concentrations values of 0.574 ng/mL and 0.581 ng/mL, respectively. The total amount of drug used by these two subjects was 42.7 g and 46.7 g respectively, which was in the lower range of the total amount of drug used (32g-78g) in the study.

**Table 11.4.4-1: Summary of Drug Concentration Levels**

	0.25% Miconazole-Nitrate Ointment (N=17)	
	Baseline	Day 7
N	0	2
Mean		0.578
STD		0.005
Min.-Max.		[0.574, 0.581]
BLQ	17 (100%)	15 ( 88%)
>BLQ	0 ( 0%)	2 ( 12%)

Intravenous miconazole has been used in children of all ages. The plasma concentrations of miconazole following IV infusion to neonates, infants (21-38 days old) and toddlers up to 2.5 years old was reported in the original NDA, clinical pharmacology review as 100-3600 ng/mL. Therefore, it is noted that the plasma concentration of miconazole obtained following topical administration of Vusion ointment ( $<$ 0.6 ng/mL) to infants aged 1-21 months old with diaper dermatitis is over 160-fold less than that obtained following IV infusion to children  $\leq$  2.5 years old.

A correlation between the observed systemic exposure, age of the patient, gender, the severity of disease, or the amount of medication used was not observed. However, the number of patients (N=2) with quantifiable plasma concentrations limits any definitive conclusions from this data.

## 3. Detailed Labeling Recommendations:

11 Page(s) Withheld

           Trade Secret / Confidential

8 Draft Labeling

           Deliberative Process

Please note that this reviewer only reviewed the pharmacokinetic component of this protocol. The medical reviewer is currently reviewing the efficacy and safety component of the protocol.

**Study No. BT0100-201-INT**

**Title of Study:** An Open Label Study to Assess the Systemic Absorption and Safety of Topically Applied 0.25% Miconazole-Nitrate Ointment in Infants with Moderate to Severe Diaper Dermatitis

**Investigators:** Nelly Paz, M.D.

**Study Centers:**

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**Study Period:** 09/2006-10/2006

**Phase of Development:** 4

**Objectives:** The objective of this study was to determine the plasma concentrations of miconazole in infants and children (who were hospitalized or in a controlled clinical setting) with moderate to severe diaper dermatitis after multiple topical applications of 0.25% miconazole-nitrate and to determine the effect of this study drug on blood biochemical laboratory parameters (i.e. chemistries and hematology) in this special patient population.

**Methodology:** This was an uncontrolled, open label, non-crossover, single-arm, multiple-dose, clinical pharmacokinetic trial designed to determine the plasma concentration of miconazole in infants and children with moderate to severe diaper dermatitis after applying topical 0.25% miconazole-nitrate ointment for 7 days. Subjects were hospitalized or in a controlled clinical setting and had baseline clinical symptoms of diaper dermatitis with a diaper dermatitis severity index score of 3-8.

There was one treatment group in this study; all subjects applied 0.25% miconazole-nitrate ointment topically for 7 days (at least 5 applications per day) whether symptoms persisted or not.

**Number of Subjects (planned and analyzed):**

Planned: 15 subjects, Analyzed: 17 subjects

**Diagnosis and Main Criteria for Inclusion:** Male and female with Fitzpatrick Skin Type I-VI, 4 weeks through 3 years of age, who wore commercial diapers day and night, with clinical evidence of diaper dermatitis and were hospitalized or were in a controlled clinical setting. Subjects were to have an overall diaper dermatitis severity index score of 3-8 at baseline visit (Study Day 0) and an overall clinical grade of at least 3 for erythema. Diaper dermatitis severity index score equaled the sum of ratings for erythema, papules or pustules, and erosions and ranged from 0 to 8.

*Reviewer's Comments: Dr. Brenda Carr reviewed (in DFS 10/12/2006) the protocol after the implementation of the protocol by the sponsor (as per the PMC timelines). The only comment she had with regards to the study population was that conducting the study in hospitalized subjects could potentially introduce confounding factors to the interpretation of the lab (i.e. the blood biochemical parameters) results, depending on the underlying illness that made for the hospitalization, and that did not appear to be specified in the protocol. This comment was faxed to the applicant on 1/30/06 by the Agency. The applicant did not modify the protocol, but they did provide the individual listing of the medical history of the subjects enrolled in the study (see medical review for further details).*

It is noted that the biochemical parameters were defined by the applicant as follows:

1. Chemistries: Glucose, BUN, uric acid, creatinine, sodium, potassium, chloride, total protein, albumin, total bilirubin, alkaline phosphatase, LDH, AST, ALT, calcium, triglyceride, total cholesterol
2. Hematology: WBC, RBC, hemoglobin, hematocrit, platelet count, lymphocytes, monocytes, eosinophils, basophils, neutrophils

**Test product, Dose and Mode of administration, Batch number:** Vusion (0.25% miconazole-nitrate ointment), topical application, (Batch number: A 11088) consisting of miconazole nitrate, USP, Zinc oxide, USP, White petrolatum, USP, (Chemoderm 1001/B) and Trihydroxystearin.

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0.25 % miconazole-nitrate ointment was topically applied by subjects' caretaker to all clinically affected areas of diaper dermatitis at each diaper change and after bathing subject (approximately 5-12 times a day) for 7 days (Study Day 0 through Study Day 7) whether symptoms persist or not. The caretaker was told not to apply any topical products (e.g. creams, ointments, lotions, disposable washcloths with fragrance and/or alcohol, etc, and/or other treatments for diaper rash including over-the counter non-prescription drugs) other than study drug on the child during the 7-day period.

**Treatment Compliance:** Designated site personnel weighed study material tubes before dispensing, Study Day 3, Study Day 5 and upon return and recorded weights in the source documents.

**Duration of Treatment:** 7 days

**Pharmacokinetic Blood Sampling:** Blood samples (0.5 ml) were obtained prior to the initial application of study drug at baseline visit (maximum 1 day prior to baseline visit), and, 4 hours after the last application (if early termination) or 4 hours after the last application on Study Day 7.

*Reviewer's Comments: The collection of blood samples at the 4 hour time-point is consistent with the time (about 4 hours) at which the peak plasma concentration of miconazole is achieved after intrabuccal administration of the oral gel. Therefore the*

*applicant is assuming that the concentration versus time curve for the topical formulation will be the same as the oral gel formulation.*

**Bioanalytical Methods:** Miconazole plasma concentrations were determined by liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS), LLOQ = 0.5 ng/mL.

**Statistical Methods:**

Demographic (age, race/ethnicity, gender) and baseline characteristics were summarized using descriptive statistics. Quantitative measures were summarized with number of subjects (n), means, standard deviations (STD), medians, minimums and maximums, while qualitative measures were summarized with frequency counts and percentages.

**Results:**

**Demographics and other Baseline Characteristics:** Seventeen (17) Hispanic/Latino subjects (5 Females and 12 Males) were enrolled and they all completed the study. The mean weight of the subjects was 17.53 pounds (range: 10-26 pounds). The mean age of the subjects was 9.19 months old (range: 1 to 21 months old). The distribution of the age of the subjects was as follows:

Age Range	Number of subjects (%)
1 to < 3 months old	2
3 to < 6 months old	5
6 to < 12 months old	4
12 to < 24 months old	6

The mean diaper dermatitis Index Score at baseline was 7.12 (range: 6-8)

**Study medication and Medication usage:** The average number of applications was 54.82 applications (range from 43 applications to 68 applications). The average total study medication usage was 51.72 grams (ranged from 32 grams to 78 grams).

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**Table 12.1.1-1: Extent of Exposure - Applications of Study Medication and Medication Usage**

		<u>0.25% Miconazole-Nitrate Ointment</u> (N=17)
<b>Number of applications</b>		
N		17
Mean		54.82
STD		7.32
Median		54.00
[Min, Max]		[43, 68]
<b>Total Applications</b>		
40-44		1 ( 6%)
45-49		3 ( 18%)
50-54		5 ( 29%)
55-69		4 ( 24%)
60-64		2 ( 12%)
65-70		2 ( 12%)
<b>Total Study Medication Usage (Grams)</b>		
N		17
Mean		51.72
STD		12.19
Median		54.00
[Min, Max]		[32, 78]

*Reviewer's Comments: Duration of exposure was the same across the development program, i.e. seven days. However, amount of individual exposure in each study was very variable since study drug was to have been applied at every diaper change. Also, the size of the diaper areas would vary according to the size of the child. It is noted that the usage amounts in the Phase 3 clinical trials as stated by Dr. Brenda Carr's review, were also very variable (ranging from 1.7 g to 98.6 g). However, it is also noted that the approved label does state that Vusion ointment should be applied at every diaper change for 7 days which is consistent with how it was studied.*

**Pharmacokinetic Results:** Fifteen of the 17 subjects had plasma concentrations of miconazole that were below the limit of quantitation (0.5 ng/mL). Two subjects (Subject 01-06 and Subject 01-17) had miconazole plasma concentrations of 0.574 ng/mL and 0.581 ng/mL, respectively.

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**Table 11.4.4-1: Summary of Drug Concentration Levels**

	0.25% Miconazole-Nitrate Ointment (N=17)	
	Baseline	Day 7
N	0	2
Mean		0.578
STD		0.005
Min.-Max.		[0.574, 0.581]
BLQ	17 (100%)	15 ( 88%)
>BLQ	0 ( 0%)	2 ( 12%)

Listing 16.2.3.4: Drug Levels  
(Page 1 of 1)

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Site-Subject	Initials	Lab ID	Concentration (ng/mL)	
			Day 0	Day 7
01-01		01	< LLOQ	< LLOQ
01-02		02	< LLOQ	< LLOQ
01-03		03	< LLOQ	< LLOQ
01-04		04	< LLOQ	< LLOQ
01-05		05	< LLOQ	< LLOQ
01-06		06	< LLOQ	0.574
01-07		07	< LLOQ	< LLOQ
01-08		08	< LLOQ	< LLOQ
01-09		09	< LLOQ	< LLOQ
01-10		10	< LLOQ	< LLOQ
01-11		11	< LLOQ	< LLOQ
01-12		12	< LLOQ	< LLOQ
01-13		13	< LLOQ	< LLOQ
01-14		14	< LLOQ	< LLOQ
01-15		15	< LLOQ	< LLOQ
01-16		16	< LLOQ	< LLOQ
01-17		17	< LLOQ	0.581

\* There was a discrepancy with the subject's initials between the CRF data and the lab data. The initials on the CRF are reported.  
LLOQ - Lower Limit of Quantitation (Theoretical Concentration 0.5 ng/mL)

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*Reviewer's Comments: The two infants with quantifiable plasma concentrations of miconazole (Subject 01-06 and 01-17) were a 7 month old male (diaper dermatitis severity index =8) and a 5 month old female (diaper dermatitis severity index =7), respectively. The total amount of drug used was 42.7 g for subject 01-06 and 46.7 g for subject 01-17. These amounts were in the lower range of the medication usage reported.*

*It does not appear that there is a correlation between the observed systemic exposure, and the age and gender of the patient, the severity of disease, or the amount of medication used. In addition, there were no adverse events reported for Subject 01-06 and 1 adverse report (Diarrhea) considered unrelated to the study drug was reported for Subject 01-17.*

**Bioanalytical Method and Assay Validation:**

<b>Method</b>	Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)
<b>Compound</b>	Miconazole
<b>Internal Standard</b>	
<b>Matrix</b>	Human Plasma
<b>Accuracy (% Bias)</b>	
<i>Within-Day</i>	6.0 to 11.0 %
<i>Between-Day</i>	7.2 to 11.4 %
<b>Precision (% CV)</b>	
<i>Within-Day</i>	3.0 to 12.3 %
<i>Between-Day</i>	3.3 to 8.2 %
<b>Standard curve range</b>	0.5 to 1.25 ng/mL ( $r^2 \geq 0.996$ )
<b>Sensitivity (LOQ)</b>	0.5 ng/mL (% CV = 6.3 and % Bias = 5.7 for N = 6)
<b>Stability</b>	Stable in human plasma after 3 freeze-thaw cycles @ ~ -80 ° C (< 10.2 % degradation) and for up to 134 days @ ~ -80 ° C (< 11.9 %) and for up to 56 days when stored frozen at -20° C (< 14.1 % degradation)
<b>Selectivity</b>	There were no significant interfering peaks observed from the blank human plasma at the retention times of miconazole or the internal standard.
<b>Conclusion</b>	Method validation is acceptable for the determination of miconazole in human plasma.

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**Applicant's Conclusions:**

Plasma concentrations of miconazole were not quantifiable ( $\leq 0.5$  ng/mL) in the majority 15/17 of infants treated with multiple daily applications of 0.25% Miconazole-Nitrate Ointment and < 1.0 ng/mL (0.574 and 0.581 ng/mL) was observed in two other infants.

*Reviewer's Comments: This reviewer concurs with the applicant's conclusions. I would also add the following comments:*

- Intravenous miconazole has been used in children of all ages. The plasma concentrations of miconazole following IV infusion to neonates, infants (21-38 days old) and toddlers up to 2.5 years old was reported in the original NDA clinical pharmacology review as 100-3600 ng/mL. Therefore, it is noted that the plasma concentration of miconazole obtained following topical administration of Vusion ointment (<0.6 ng/mL) to infants aged 1-21 months old with diaper*

*dermatitis is considerably less (at least 160-fold less) than that obtained following IV infusion to children  $\leq 2.5$  years old.*

- *A correlation between the observed systemic exposure, age of the patient, gender, the severity of disease, or the amount of medication used was not observed. However, the number of patients (N=2) with quantifiable plasma concentrations limits any definitive conclusions from this data.*

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Abi Adebawale  
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Lydia Velazquez  
8/29/2008 12:39:54 PM  
BIOPHARMACEUTICS

# Memo

**Date:** 5/24/2005

**To:** Dr. Brenda Carr and Dr. Markham Luke (OND-540)

**From:** Dr. Abimbola Adebawale and Dr. D. Bashaw (DPE-III, OCPB)

**RE:** Clinical Pharmacology and Biopharmaceutics Study in the Pediatric Patient Population for NDA 21-026 [Zimycan Ointment (consisting of miconazole nitrate 0.25 %, zinc oxide 15 % and white petrolatum 81.35 %) indicated for Diaper Dermatitis complicated by candidiasis]

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This memo is an amendment to the two previous clinical pharmacology and biopharmaceutics reviews (dated 4/21/99 and 05/02/05) for this NDA. This memo is being written because the chemistry review team recently identified information in the NDA that the petrolatum used in the to-be-marketed (TBM) formulation differs from that in the lot used in the in vivo biostudy. Since petrolatum in this product is both a structure forming ingredient and an active ingredient, changes in the properties of petrolatum can potentially affect both the safety and efficacy of this product.

The application in question is a re-submission following a non approvable (NA) letter of July 24<sup>th</sup>, 2000. At the time of the NA letter there were no clinical pharmacology and biopharmaceutics (CPB) deficiencies identified and the applicant did not submit any new CPB studies or information in this application. However, they did include a revised label which was reviewed (by Dr. Adebawale) and found acceptable provided the applicant agreed with the proposed changes (review dated 05/02/05).

On May 18<sup>th</sup>, 2005, the chemistry review team identified that there were differences in the chain length and branching in the petrolatum used in the diaper dermatitis percutaneous absorption study (Study 12966.37C) versus what was used in the applicant's pivotal clinical study and TBM product. The chemistry team also noted that a comparison of the two formulations failed the in vitro release study as described in the SUPAC-SS guidelines.

Although Study 12966.37C was previously reviewed by Dr. Tandon (review dated 4/21/99) and found acceptable. The only information provided at that time which was noted in her review was that the formulation differed only in the removal of a fraction from the fragrance.

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This change in petrolatum was conveyed to HFD-540 management and to the Division of Pharmaceutical Evaluation-III on 5/19/05. After considering the information provided by the chemistry team, Dr. Bashaw then sent out the following statement on 05/19/05 to the clinical division, DPE-III management and the chemistry review team by e-mail. Inserted below is a copy of the contents of the e-mail:

*Please note that at this time I have not been able to raise this issue with my management due to the lateness of the issue being raised last night and an anti-viral advisory committee this morning. Because of your short timeline I am sending the following to you and to my management at the same time. Whether or not they will want to weigh in on the issue is unknown to me, however, I did want to respond to your request with our best guidance at this time.*

*After consideration of the issues surrounding miconazole I have come to the conclusion that a new in vivo biostudy would be required. This is based on discussions with both the review Chemist Dr. Saleh Turujman and the Medical Officer Dr. Brenda Carr. From a chemistry point of view petrolatum is present both as a skin protectant and as a structure forming excipient. In fact petrolatum is given as an example of a structure forming excipient in the SUPAC-SS guidance document (see below):*

**Structure Forming Excipient:** *An excipient which participates in the formation of the structural matrix which gives an ointment, cream or gel etc., its semisolid character. Examples are gel forming polymers, petrolatum, certain colloidal inorganic solids (e.g., bentonite), waxy solids (e.g., cetyl alcohol, stearic acid), and emulsifiers used in creams.*

*The change in petrolatum from biostudy to to-be-marketed formulation, according to Dr. Turujman, is in the branching of the alkyl chains present in petrolatum. This change in the underlying structure of petrolatum can have a significant impact on the release and migration of drug substances through the formulation, thus affecting the rate of presentation/exposure/bioavailability of miconazole to the skin. This is clearly an issue both for safety and efficacy of the product.*

*Normally, the role of clinical pharmacology/biopharmaceutics in the dermatology area is to provide safety information by determining systemic absorption. In other cases we have allowed sponsors who have used the wrong patient populations (i.e. healthy subjects instead of subjects with acne) to obtain in vivo bioavailability data as a Phase IV based on the clinical safety data determination from the Phase III trials. In the case of the acne products, however, the final formulation was used-but in a patient population that might not be representative of the target population. In the current situation, according to Dr. Carr, the ITT population is less than 120 subjects and there is an expectation that the in vivo pk data would inform the safety population. Given the target population (infants) and the conditions of use (on inflamed skin subject to high humidity and occlusion) it would establish a worrisome standard to allow this product to go*

*forward without a proper determination of in vivo bioavailability from the to-be-marketed formulation at this time.*

*Based on the facts presented regarding both the changes in petrolatum and the clinical conditions of use of this product, it is my recommendation as the team leader of the Clinical Pharmacology/Biopharmaceutics review team assigned to the Dermatology Division that an additional in vivo biostudy be required prior to marketing.*

On May 19<sup>th</sup>, 2005, a teleconference was held between the Agency and the applicant to discuss our concerns about the lack of systemic exposure data with the to-be-marketed formulation. At this teleconference, Dr. Arzu Selen (Deputy Director, Division of Pharmaceutical Evaluation-III) was in attendance, and concurred with the e-mail Dr. Bashaw had sent to the division. During the teleconference the applicant was informed of our concerns and asked to provide information to alleviate our concern with a deadline of COB next day. The applicant sent a response to the Agency on May 20<sup>th</sup>, 2005 at 5:58 PM. Due to the lateness in the day, this was given a cursory review by Dr. Bashaw on the same day after which a brief telecom was held between the Agency and the applicant requesting additional information. The additional information was submitted on May 20<sup>th</sup>, 2005 at 7:12 PM.

On May 23<sup>rd</sup>, 2005, following examination of the information sent by the sponsor, Dr. Bashaw then sent a statement to the clinical division, chemistry review team and DPE-III management by e-mail. Inserted below is a copy of the contents of the e-mail:

*In a follow up to the material the sponsor submitted last Friday, a brief telecon was held between myself, Mille Wright, and the sponsor. In this telecon additional information was requested relating to in vitro test results using the Franz diffusion cell apparatus that were referred to in the material submitted Friday afternoon. This material was submitted on Friday evening. In it there are the results of in vitro testing looking at various manufacturing and formulation factors. Of interest is that this report was prepared at the request of Dr. Decamp (former FDA Derm Div. Chemistry Team leader). The results, while not strictly applicable, indicate that variations in the source of petrolatum have an impact on the release of miconazole from the matrix, to the point where the release rates are outside the limits established by SUPAC-SS.*

*Thus these studies confirm that variations in the petrolatum itself are sufficient to result in changes in release even though both sources of petrolatum meet USP specifications.*

*Some consideration should be given to eventual communication of this information to the USP for their consideration in the petrolatum monograph.*

A team meeting was then held in the afternoon of May 23<sup>rd</sup> to decide what action would be taken for this NDA. At the meeting, the chemistry review team affirmed that there were differences in the petrolatum and that the release rates from the different formulations were outside the limits of SUPAC-SS. The medical team, specifically Dr.

Carr, affirmed that although the applicant had provided safety data, there was no systemic monitoring, therefore the systemic exposure data with the to-be-marketed formulation would be needed. As an assessment of in vivo bioavailability is a component of the safety evaluation of the product, this study should be conducted prior to approval. Alternatively, the sponsor could also provide additional information to address the issue as to why these changes in the petrolatum and in the in vitro testing would not be significant in the target population. However, the assessment of the adequacy of this information would be a review issue and if found inadequate an in vivo biostudy would still be necessary. It was then decided that the action that would be taken is a non-approvable (NA).

***The following is the statement from the Division of Pharmaceutical Evaluation III that is to be included in the NA action letter***

Based on the information provided by the chemistry review team, the in vitro release characteristics of the two formulations (under the conditions of SUPAC-SS testing) are outside the acceptance limits. Given that petrolatum is both a structure forming ingredient and an active ingredient (i.e., skin protectant) a new in vivo biostudy using the to-be-marketed/clinically studied formulation is needed. As an assessment of in vivo bioavailability is a component of the safety evaluation of the product, this study should be conducted prior to approval.

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## Office of Clinical Pharmacology and Biopharmaceutics Review

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<b>NDA #</b>	21-026
<b>Submission Date (s)</b>	November 24 <sup>th</sup> , 2004
<b>User Fee Date</b>	May 24 <sup>th</sup> , 2005
<b>Brand Name</b>	Zimycan
<b>Generic Name</b>	Miconazole Nitrate Zinc Oxide/Petrolatum
<b>Formulation; Strength(s)</b>	Ointment; miconazole nitrate 0.25 %, zinc oxide 15 % white petrolatum 81.35 %
<b>Reviewer</b>	Abimbola Adebawale Ph.D.
<b>Team Leader</b>	Raman Baweja Ph.D.
<b>OCPB Division</b>	DPE-III
<b>OND Division</b>	HFD-540
<b>Applicant</b>	Barrier Therapeutics, Inc. Princeton, NJ 08540
<b>Submission Type; Code</b>	Resubmission
<b>Pharmaceutical Class</b>	Imidazole antifungal
<b>Indication</b>	Treatment of diaper dermatitis complicated by candidiasis

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### 1. Executive Summary:

This submission is an NDA amendment submitted in response to the non approvable (NA) letter of July 24th, 2000. Barrier Therapeutics, Inc. is submitting the current New Drug Application (NDA) Amendment to obtain approval for a new prescription product, 0.25 % miconazole nitrate ointment (Zimycan<sup>TM</sup>) for the treatment of diaper dermatitis complicated by candidiasis.

This NDA was previously submitted to the FDA by Johnson and Johnson Consumer Products Worldwide on August 24<sup>th</sup>, 1998. The applicant acquired this NDA from Johnson and Johnson Consumer Products Worldwide on June 21, 2002. At the time of ownership transfer, this NDA was the subject of the non-approvable (NA) letter dated July 24, 2000.

The applicant did not submit any new clinical pharmacology and biopharmaceutics studies or information in this application however they did include a revised label which would be the subject of this review.

#### 1.1 Recommendation:

From a Clinical Pharmacology and Biopharmaceutics perspective, the proposed label included in this submission is acceptable provided that the applicant agrees with the recommended labeling changes below (additions to the applicant's proposed label are in bold italics):

b(4)

1.2 Phase IV Commitments: Not Applicable

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The Clinical Pharmacology and Biopharmaceutics (CPB) information submitted in the original NDA was reviewed by OCPB (review date April 21, 1999) and found to be acceptable. There were no CPB deficiencies in the NA letter (dated July 24, 2000).

A brief summary of the studies reviewed by OCPB are provided below:

The applicant only conducted one in vivo study (# 12966.37C) in infants to evaluate percutaneous absorption of topical miconazole nitrate. Other information on the pharmacokinetics (percutaneous absorption in adults, intravaginal, IV and oral absorption, distribution, metabolism, and excretion) of miconazole nitrate was based on earlier research by Janssen Research, Belgium or based on literature references.

The applicant also conducted an in vitro permeation study upon request to investigate the release of elemental zinc from the ointment using occluded Franz Cell model and human cadaver skin. This study was conducted to fulfill the in vivo/in vitro bioavailability requirements for all active ingredients in a dosage form. This was because it was decided that zinc oxide may also have some therapeutic effect even though it was included as a vehicle in the formulation.

**Signatures**

Reviewer:

\_\_\_\_\_  
Abimbola Adebawale, Ph.D.  
Clinical Pharmacology Reviewer  
Division of Pharmaceutical Evaluation III  
Office of Clinical Pharmacology and Biopharmaceutics

Team Leader Concurrence:

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Ray Baweja, Ph.D.  
Team Leader  
Division of Pharmaceutical Evaluation III  
Office of Clinical Pharmacology and Biopharmaceutics

**2. Question Based Review (QBR)**

There is no QBR for this submission since the applicant did not submit any new clinical pharmacology and biopharmaceutics information. The proposed label is reviewed in the next section.

**3. Detailed Labeling Recommendations:**

The sponsor has proposed the following wording in the pharmacokinetics section under the "Clinical Pharmacology" section of the proposed label:

**CLINICAL PHARMACOLOGY**

**b(4)**

**Reviewer's proposed revised label**

*(Deletions are strikethroughs and additions are bolded italics)*

**4. Appendices**

**4.1 Package Insert (Proposed and Annotated)**

**b(4)**

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b Draft Labeling

       Deliberative Process

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Raman Baweja  
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BIOPHARMACEUTICS

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**Office of Clinical Pharmacology and Biopharmaceutics Review**

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<b>NDA #</b>	21-026
<b>Submission Date (s)</b>	August 15 <sup>th</sup> , 2005; August 25 <sup>th</sup> , 2005, October 18 <sup>th</sup> , 2005, November 14 <sup>th</sup> , 2005
<b>User Fee Date</b>	February 16 <sup>th</sup> , 2006
<b>Brand Name</b>	Vusion™
<b>Generic Name</b>	0.25 % miconazole nitrate, 15 % zinc oxide and 81.35 % white petrolatum
<b>Formulation; Strength(s)</b>	Ointment
<b>Reviewer</b>	Abimbola Adebawale Ph.D.
<b>Team Leader</b>	Dennis Bashaw Pharm.D.
<b>OCPB Division</b>	DCP3
<b>OND Division</b>	OND-540
<b>Applicant</b>	Barrier Therapeutics, Inc. Princeton, NJ 08540
<b>Submission Type; Code</b>	Resubmission
<b>Pharmaceutical Class</b>	Imidazole antifungal
<b>Indication</b>	Treatment of diaper dermatitis complicated by candidiasis

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**1. Executive Summary:**

This NDA amendment is submitted as a complete response to the non approvable (NA) letter issued to the applicant on May 24<sup>th</sup>, 2005. This New Drug Application (NDA) Amendment is for the approval of a new prescription product, 0.25 % miconazole nitrate ointment (Vusion™) for the treatment of diaper dermatitis complicated by candidiasis in immunocompetent pediatric patients 4 weeks and older.

This NDA was previously submitted to the FDA by Johnson and Johnson Consumer Products Worldwide on August 24<sup>th</sup>, 1998. The applicant acquired this NDA from Johnson and Johnson Consumer Products Worldwide on June 21, 2002. At the time of ownership transfer, this NDA

was the subject of the non-approvable (NA) letter dated July 24, 2000. The NDA was then re-submitted on November 24<sup>th</sup>, 2004 and the application was again the subject of another non approvable letter (dated May 24<sup>th</sup>, 2005) due to inadequate information.

Basically, the NA letter stated that there was insufficient information to characterize the systemic exposure to miconazole from this product. Although the applicant used the to-be-marketed formulation in the clinical studies that were conducted, the medical reviewer stated that the information was not sufficient to fully evaluate the safety of the drug product especially with regards to hepatically related adverse effects which may be related, to a certain degree, to plasma levels. In addition, the product used in the pharmacokinetic study (a component of the safety evaluation) was different from the to-be-marketed product in terms of the grade of white petrolatum used.

On July 14<sup>th</sup>, 2005, the Agency had a meeting with the applicant to provide clarification for the basis of the deficiencies cited in the May 24<sup>th</sup>, 2005, non approvable letter. At the meeting the agreements reached pertaining to OCPB were as follows:

1. The Sponsor will submit a complete response which should include systemic absorption information of miconazole in the indicated population that supports safety and,
2. The sponsor will submit a draft protocol for a Phase 4 pharmacokinetic (PK) study of the to-be-marketed product in infants with liver function testing (e.g. blood chemistry).

The additional systemic absorption data and information submitted by the sponsor to support safety and meet the requirements of the complete response will be discussed in this review. In addition, the applicant submitted the draft PK protocol to the IND ( ) on October 18<sup>th</sup>, 2005 and this will be reviewed separately.

#### 1.1 Recommendation:

The systemic exposure information provided by the applicant following topical, topical oral and intravenous administration of miconazole in the pediatric population was adequate to support safety. The data demonstrated that the systemic exposure of miconazole 0.25 % ointment containing petrolatum is minimal when compared to the systemic exposure obtained in children (neonates to 2.5 years old) following administration of currently marketed intravenous and topical oral drug products (Europe , not US).

**b(4)**

Although suggestive of minimal systemic exposure of miconazole following topical application, a definitive evaluation of the systemic exposure of the to-be-marketed formulation would still be needed (especially in view of the target population (infants) and the use of it under occlusion (i.e. diapers, training pants, etc.)). In light of this, the applicant has submitted (on 10/18/05) a draft protocol to the IND (# 21-542) for the Phase 4 pharmacokinetic study of the to-be-marketed product (which was also used in the clinical trials in the NDA) containing Petrolatum. This submission is acknowledged and the protocol is currently under review.

**b(4)**

Therefore, from a clinical pharmacology and biopharmaceutics perspective, the applicant has adequately met the requirements for the complete response agreed upon at the July 14<sup>th</sup> meeting

and their application is acceptable. We have the following labeling recommendations (strike through are deletions and additions to the applicant's proposed label are in bold italics):

**Pharmacokinetics:**

The topical absorption of miconazole from ~~VUSION~~ *an Ointment containing 0.25 % miconazole nitrate, 15 % zinc oxide and 81.35 % white petrolatum* was studied in male and female infants (n=18) with diaper dermatitis ranging in age from 1 month to 12 months. After application at every diaper change for 7 days, the plasma concentrations of miconazole were nondetectable (<1 ng/mL) in the majority (15/18) of patients and ranged from 3 to 3.8 ng/mL in the other 3 remaining patients.

1.2 Phase IV Commitments: A phase 4 pharmacokinetic study of the to-be-marketed product in infants with liver function testing i.e. blood chemistries (see comments in recommendation).

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings:

In this submission, the applicant provided previously submitted data on the pharmacokinetics and bioavailability of miconazole following topical and intravenous administration in adults and children. Since this data had already been reviewed by Dr. Tandon in the original submission (see Appendix for a brief regulatory history), they were not reviewed again.

A brief overview is provided in the review. Basically the data indicated that the systemic exposure of miconazole following topical administration of the 0.25 % miconazole ointment to children (aged 1-12 months) with diaper dermatitis is minimal when compared to that obtained following IV infusion to children (neonates to age 2.5 years old). In addition the applicant provided information on the systemic exposure of Daktarin oral gel which is currently marketed in Europe for use in infants less than 2 years old. This data provided further support of the minimal systemic exposure of miconazole obtained following topical application of the 0.25 % miconazole ointment.

Although the information provided is suggestive of a minimal systemic exposure of miconazole compared to other routes of administration even when the petrolatum grade is changed, it does not provide a definitive assessment of the systemic exposure of the to-be-marketed formulation. Such a determination is necessary in light of the results of in vitro release testing showing a different rate of miconazole release for different grades of petrolatum. While the clinical studies do indicate that the product is efficacious, the potential for hepatic related adverse events was not properly assessed in the clinical studies program. Based on the aforementioned, the applicant has proposed to conduct a Phase 4 pharmacokinetic study with hepatic enzyme monitoring with the to-be-marketed formulation.

**Signatures**

Reviewer:

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Abimbola Adebawale, Ph.D.  
Clinical Pharmacology Reviewer  
Division of Clinical Pharmacology 3

Office of Clinical Pharmacology and Biopharmaceutics

Team Leader Concurrence: \_\_\_\_\_

Dennis Bashaw, Pharm.D.  
 Team Leader  
 Division of Clinical Pharmacology 3  
 Office of Clinical Pharmacology and Biopharmaceutics

**2. QBR**

***What is the difference between the formulation used in the percutaneous absorption study (# 12966.37C) and the to-be-marketed formulation?***

The table below provides a summary of the comparison of the two formulations:

Formula # F 100 – Percutaneous Absorption study # 12966.37C	Formula # F114 - to be marketed formulation
0.25% Miconazole Nitrate 15% Zinc Oxide	0.25% Miconazole Nitrate 15% Zinc Oxide
81.35% Petrolatum <ul style="list-style-type: none"> <li>• Melting Point ASTM D127, °C = 56</li> <li>• Consistency, ASTM D937 = 168</li> <li>• Congealing Point, ASTM D938, °C =52</li> <li>• Viscosity @ 100 °C, cSt =12</li> <li>• Same EP and USP Specification tube contains 75 mg of miconazole</li> </ul>	81.35% Petrolatum <ul style="list-style-type: none"> <li>• Melting Point ASTM D127 °C =59</li> <li>• Consistency, ASTM D937 = 191</li> <li>• Congealing Point, ASTM D938, °C = 52</li> <li>• Viscosity @ 100 °C, cSt =9.2</li> <li>• Same EP and USP Specifications tube contains 75 mg of miconazole</li> </ul>
Human Exposure <ul style="list-style-type: none"> <li>• Daktozin [European Marketed Product since 1993].</li> </ul>	Human Exposure <ul style="list-style-type: none"> <li>• Pivotal clinical study # BT 100 USA/001</li> <li>• All other supportive phase III studies.</li> </ul>

b(4)

*Reviewer's Comments: The table above shows that the only difference between the formulations (# F100) used in the in vivo percutaneous absorption study and the to-be-marketed formulation (# F114) is the grade of the petrolatum. Although the petrolatum grades*

*( ) were of the same EP and USP specification, they showed differences in their melting point, consistency and hence viscosity too. According to the reviewing chemist, these differences are due to a difference in the degree of alkyl side chain branching in the two sources of petrolatum. The impact of the observed differences in viscosity may have contributed to differences in the release rates in the in vitro studies conducted by the applicant. However, the effect of these differences in the grade of petrolatum on the systemic exposure of miconazole ointment when applied to infants is currently unknown.*

b(4)

***What is the systemic absorption information of miconazole in the indicated population that supports safety provided in this submission?***

The applicant provided the following systemic absorption in the targeted population in this submission:

1. A summary of the results of the pediatric percutaneous absorption study (Study Number 12966.37C) conducted in infants (N = 24) with moderate to severe dermatitis who had been hospitalized for treatment of systemic pathology (primarily gastroenteritis) aged 1-12 months. Miconazole 0.25 % was applied to the clinically affected area at each diaper change for 7 days and blood samples were taken prior to treatment on Day 1 and on Day 7. This study report was previously submitted in the original NDA submission of 8/24/1998, reviewed by Dr. V. Tandon on 4/21/99 and found acceptable therefore they will not be reviewed again. A brief overview of the conclusions of her review is inserted below:

The results of Study 12966.37C indicated that the plasma concentrations of miconazole were nondetectable (< 1 ng/mL) in 15 of 18 patients and < 5 ng/mL in the remaining three. In 4/5 infants treated with multiple daily applications of 2 % miconazole nitrate cream, miconazole concentrations ranged from 5.2 to 7.4 ng/mL and was nondetectable in one subject. Blood concentrations after topical use are at least 50 to 450-fold lower than the range of maximal blood concentrations of 400-3600 ng/mL reported in children administered 7-10 mg/kg intravenously.

*Reviewer's Comments: This proposed label by the applicant is based totally on the data obtained from the study described above that used topically applied miconazole, therefore it is recommended that the product should not be referred to as Vusion in the label since the grade of petrolatum is different.*

2. A summary of the literature on the absorption of miconazole following intravenous administration: This information had also been previously submitted and reviewed by Dr. Tandon. Inserted below is the conclusion of her review:

...Intravenous miconazole has been used in children of all ages, including neonates and newborns. The infusion doses in these studies ranged from 3.8-16.6 mg/kg. Plasma concentrations ranged from 100-3600 ng/mL.

*Reviewer's Comments: The ages of the pediatric population administered the IV infusion ranged from neonates, infants (21-38 days old) to 2.5 years old. The total daily dose administered ranged from 10-63 mg/kg/day. This information was used to support the applicant's conclusion that given a comparable dose of miconazole 0.25 % topically (~ 12.5 mg per day), the plasma concentration of miconazole obtained is considerable less than that obtained following IV infusion to children.*

3. A comparison of the systemic exposure of miconazole (0.25 %) ointment and miconazole oral gel (currently approved in Europe): The applicant provided the Daktarin® oral gel package insert in this submission. This is new information for this submission. Reproduced in the table below is a summary of a comparison of the two products:

<b>Name of Product</b>	<b>Miconazole 0.25 % ointment</b>	<b>Daktarin ® Oral Gel</b>
<b>Regulatory Status</b>	Not Approved	Approved in Europe, UK (Since 1993)
<b>Qualitative and Quantitative Composition</b>	2.5 mg miconazole per gram ointment; 7.5 mg miconazole per tube	20 mg miconazole per gram gel; 300-1600 mg of miconazole per tube
<b>Therapeutic Indication</b>	Adjunctive treatment of diaper dermatitis only when complicated by candidiasis in immunocompetent pediatric patients 4 weeks and older	Oral treatment and prevention of fungal infections of the oropharynx and gastrointestinal tract, and of super infections due to Gram-positive bacteria
<b>Dose</b>	~ 12.5 mg miconazole applied topically per day for 7 days	Children under 2 years old get 2.5 mL twice per day for 5-12 days. This is ~100 mg miconazole per day
<b>Systemic Exposure</b>	3.0 – 3.8 ng/mL	1000 ng/mL after 1 gram (i.e. 1000 mg) per day

*Reviewer's Comments: The comparison in the table above suggests that the systemic absorption of miconazole following topical application is about 30 fold less than that obtained following oral topical administration to children under 2 years of age. This information provides further support of the safety of miconazole 0.25 % ointment in this population. Although suggestive of a minimal systemic exposure following topical application of miconazole 0.25 % ointment, it does not provide a definitive assessment of what the systemic exposure of the to-be-marketed formulation of miconazole 0.25 % ointment will be under its conditions of use.*

**3. Detailed Labeling Recommendations: (See under Recommendations in Section 1.1)**

**4. Appendices**

**4.1 Package Insert (Proposed)**

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**Brief Regulatory History:**

Submission Date	CPB data/information	Product Used	CPB Data acceptable (Y/N)Regulatory Action	CPB Deficiency
8/24/98, 3/1/99, 3/30/99	Percutaneous absorption study of barrier's drug product (0.25 %	Formula F100 containing grade of	Yes. Reviewer's conclusions were that "blood concentrations	None

b(4)

	<p>miconazole/white petrolatum/zinc oxide ointment) was conducted in infants (aged 1-12 months) with diaper dermatitis associated with gastroenteritis. The drug product was applied at each diaper change for 7 days. Blood samples were taken prior to Day 1 and on Day 7. (Study # 12966.37C)</p> <p>Study also included 5 subjects who received applications of 2 % miconazole cream at each diaper change for 7 days.</p>	petrolatum	<p>after topical use are at least 50 to 450 fold lower than the range of maximal blood concentrations of 400-3600 ng/mL reported in children administered 7-10 mg/kg intravenously. Also data was included of IV miconazole in children for all ages including neonates and newborns. The infusion doses in these studies ranged from 3.8-16.6 mg/kg. The plasma concentrations ranged from 100-3600 ng/mL.</p>	
11/24/2004	None, only a revised label	NA	Labeling recommendations	None
5/20/2005	<p>On 05/18/2005, the chemistry review team discovered that the formulation used in the PK study was not the same as the to-be-marketed formulation (TBMF). The formulation differed in the grade of petrolatum. The chemist's also noted that a comparison of the two formulations (PK and clinical) failed the in vitro release test (SUPAC-SS).</p>		<p>No. A Memo to amend the two previous CPB reviews above was written. This Memo stated that an <i>in vivo</i> bioavailability study using the TBMF is needed prior to approval.</p>	<p>The language included in the NA letter of 05/24/05 was as follows: Insufficient information to characterize the systemic exposure to miconazole from the TBMF. Characterization of the systemic exposure to miconazole is a component of the safety evaluation of the product.</p>

	Applicant sent a response to the Agency's concern about the lack of systemic exposure data with the to-be-marketed formulation.			
06/20/2005	Briefing package for end of review. Meeting (on 07/14/2005) between the Agency and the sponsor to clarify the basis for the deficiencies listed in the May 24 <sup>th</sup> , NA letter. Sponsor provided additional information on systemic exposure of miconazole in the target population	NA	Data gave better understanding of the systemic exposure of miconazole in the pediatric population where safety has been adequately characterized.	Agreement was for sponsor to submit a complete response that would include systemic absorption information of miconazole in the indicated population that support safety.  Also a draft protocol for a phase 4 pharmacokinetic study of the to-be-marketed product with liver function testing.

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Table 1. Summary of Pharmacokinetic Studies and Results

Reference Number	Study Type	Subjects	Route of Administration	Dose (mg)	Dose Regimen	Peak Miconazole Concentration (ng/mL)	Tmax (hr)	Cumulative Excretion		NDA/OTC/Patent No.	
								Urine <sup>a</sup>	Feces <sup>a</sup>		
5	A	Pediatric	Topical (0.25%) Topical (2%)	10 <sup>b</sup>	7 Days	<1.0-3.8 <sup>c</sup> 5.2-7.4 <sup>c</sup>	-	-	-	1.11 006 00067	
6,7	M,E	Adult	Oral	50 <sup>d</sup>	Single Dose	290 - 390 <sup>e,f</sup>	4	17.8	43.8	1.11 006 00162	
	E	Adult	Oral	1000 <sup>e</sup>	Day 2 and 15 <sup>e</sup>	1.8 - 2.2 103 <sup>e,f</sup>	4	13.0	49.6	1.11 006 00169	
	E	Adult	Topical (2%)	20	Single Dose	2.6 <sup>e,f</sup>	-	0.35	-		
11	A	Adult	Topical (2%)	100	Single Dose	<10 <sup>g</sup>	ND	-	-	1.11 006 00313	
12	A	Adult	Intravaginal	100	7 Days	8.84 <sup>h,i</sup>	10-12	1.03%	0.85%	1.11 006 00316	
13	A	Adult	Intravaginal	100	7 Days	12.68 <sup>h,i</sup>	12	-	-	1.11 006 00318	
				200	3 Days	8.84 <sup>h,i</sup>					
14	A	Adult	Intravaginal	1200	Single Dose	10.4 <sup>f</sup>	6-24	-	-	1.11 006 00365	
15	A,D	Adult	Intravenous	522	Single Dose	2020 9100	0.25	-	-	1.11 006 00370	
16	A,D,E	Adult	Oral Tablet	500	Single Dose	1240	2-4	-	-	1.11 006 00376	
			Oral Gel	500	Single Dose	1790					
17	CR	Pediatric	Intravenous	5	Single Dose	1600	-	-	-	1.11 006 00385	
18	CR	Pediatric	Intravenous	3.8 <sup>j</sup>	Multiple doses	530	2.0	-	-	-	1.11 006 00386
			Intravenous	6.9 <sup>j</sup>	Multiple doses	1260	2.0				
			Intravenous	6.0 <sup>j</sup>	Multiple doses	650	2.0				
			Intravenous	4.0 <sup>j</sup>	Multiple doses	710	1.0				
19	CR	Pediatric	Intravenous	4.0 <sup>j</sup>	6 Days	400	0.5	-	-	-	1.11 006 00390
				7.4 <sup>j</sup>	7 Days	400	0.5				
20	CR	Pediatric	Intravenous	8.9 <sup>j</sup>	Multiple doses	1600	1.0	-	-	-	1.11 006 00394
				10.5 <sup>j</sup>	Multiple doses	3600	1.0				

A=Absorption

D=Distribution

M=Metabolism

E=Excretion

CR = Case report from published literature

<sup>a</sup> Mean percent of administered radioactivity recovered (see text for time period)

<sup>b</sup> Estimated dose based on regimens used in pivotal clinical trials (90<sup>th</sup> percentile)

<sup>c</sup> Range (limit of detection < 1 ng/mL)

<sup>d</sup> 50 mg <sup>3</sup>H miconazole single dose (with 6 day washout)

<sup>e</sup> Days 2 and 15: Single dose of 250 mg <sup>3</sup>H-miconazole + 750 mg unlabelled miconazole q.d.

<sup>f</sup> ng equiv/mL (total plasma radioactivity)

<sup>g</sup> Limit of detection 10 ng/mL

<sup>h</sup> After last dose

<sup>i</sup> Mean value

<sup>j</sup> Mg/kg + 1000 mg unlabelled miconazole b.i.d.

Days 1, 3-14, 16-28: 1000 mg unlabelled miconazole t.i.d.

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**Table 8. Summary of Miconazole Plasma Concentrations  
Following Intravenous Infusion in a Pediatric Population**

Age	Weight (kg)	Dose Per Infusion <sup>a</sup> (mg/kg)	Miconazole Blood Concentration		Total Daily Dose (mg/kg/day)	Ref
			Time post infusion	Concentration (ng/mL)		
Neonate	0.89	5	1	1600	10	17
Infant 21 Days	0.71	3.8	2	530	11.4	18
			6	190		
			6	270		
Infant 38 Days	4.87	6	2	650	18	18
			6	180		
Infant 35 Days	1.2	4.0	0 <sup>b</sup>	200		19
			0.5	400		
			-2	200		
			7.4	100		
			0.5	400		
8 Months	19	10.5	2	200	32-63	20
			1	3600		
			7	2000		
16 months	36	11.1	7	810	17-33	20
			1	5000		
1.5 Years	9.5	8.9	1	1600	27	20
			7	250		
2.5 Years	12	16.6	7	400	50-60	20

<sup>a</sup> Infusion times varied from 15 mins. to 8 hrs.

<sup>b</sup> After six days treatment

<sup>c</sup> After two days treatment

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1/18/2006 04:07:48 PM  
BIOPHARMACEUTICS

John P. Hunt  
1/18/2006 04:32:33 PM  
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## Clinical Pharmacology/Biopharmaceutics Review

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NDA: 21-026 SUBMISSION DATE: 8/24/98, 3/1/99  
3/30/99

PRODUCT: PEDIASTAT™  
(Miconazole Nitrate 0.25% ointment)

SPONSOR: Johnson & Johnson Consumer Co,

REVIEWER: Veneeta Tandon, Ph.D.

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### Review of a NDA

#### I. Background

PEDIASTAT™ Diaper rash ointment contains the synthetic antifungal agent, miconazole nitrate (0.25%) in a zinc oxide (15%) and petrolatum base for dermatologic use. It is indicated for the treatment of moderate to severe dermatitis where *Candida albicans* may be a contributing factor. Diaper rash, also called diaper dermatitis, is an acute inflammatory disorder affecting the region of the skin covered by the diaper.

Miconazole nitrate, commonly available on the market at a 2% concentration, is one of the most widely used antifungal agents and has not created any safety concerns. PEDIASTAT™ is developed with a 0.25% of miconazole nitrate to further optimize safety in infants. Topical 0.25% miconazole nitrate has been commercially available outside United States since 1991.

Zinc oxide has been used for many years in topical formulations such as sunscreens, skin protectants for diaper rash, hemorrhoids etc. The concentrations used in diaper rash ointment range from 10-40% (e.g DESITIN® ointment). The recommended daily dietary allowances for Zn for infants 0-1 years old is 5 mg and for 1-10 years old is 10 mg of Zn.

#### *Dosage and Administration:*

PEDIASTAT™ diaper rash ointment will be made available as 30 g tubes. It should be applied to the entire affected area with fingertips at each diaper change and should not be rubbed in the area.

b(4)

#### II. Recommendation

The application is acceptable from the Clinical Pharmacokinetics/biopharmaceutics standpoint. The applicant has demonstrated very low exposure of miconazole from the product on topical application. Adequate information from the literature has been provided on the metabolism, distribution and elimination of miconazole from oral and

intravenous dosage forms of the product. The reviewer recommends approval from the biopharmaceutics standpoint.

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	B. Adult percutaneous absorption					*	*	*	*	4
	C. Intravaginal absorption			*	*	*	*	*	*	4
	D. Other (from literature)			*	*	*	*	*	*	5
	Distribution (from literature)	*	*	*	*	*	*	*	*	5
	Metabolism (from literature)	*	*	*	*	*	*	*	*	6
	Excretion (from literature)	*	*	*	*	*	*	*	*	6
	In vitro Study	*	*	*	*	*	*	*	*	6
VI.	Conclusions	*	*	*	*	*	*	*	*	8
	Appendix	*	*	*	*	*	*	*	*	9

### III. Formulation

This formulation given below is used for all clinical trials. The formulation intended for commercial use (Formulation No. 710-63) was used in the Phase III clinical trials. Formulation No. 710-63 differs from the formulation used in the Phase I and II studies (Formulation No. 710-58), only in the removal of a fraction from the fragrance (1001).

b(4)

<u>Component</u>	<u>%w/w</u>	<u>Role</u>
Miconazole Nitrate, USP	0.25	Active
Zinc Oxide, USP	15.00	Vehicle
White Petrolatum, USP	81.35	Vehicle
(Chemoderm 1001/B)		Fragrance
Trihydroxystearin		

b(4)

#### *Reviewer's Comment*

*The sponsor has indicated 15% zinc oxide as a vehicle in the formulation of PEDLASTAT™. This was questioned after the submission of the NDA and the sponsor was requested to perform an in vitro permeation study to investigate the release of elemental zinc from the formulation. The results of this have been provided in the review*

*of the application. Zinc oxide will not be active against Candida albicans, however, may have therapeutic effect in the treatment of diaper rash. Zinc oxide is known to provide additional physical barrier by forming a protective coating over the skin or mucous membrane that serves to reduce further effects of irritants on affected area. Zinc oxide in the range of 10-40% is present in many other diaper rash treatments and in some constitute the only active ingredient.*

#### **IV. Analytical Validation**

Analytical methods were implemented to support clinical studies in adult volunteers and infant patients. Liquid Scintillation Counting (LSC) was used to assess the topical absorption of the various <sup>3</sup>H-miconazole preparations. The specific determination of miconazole in human plasma was accomplished using gas chromatography (GC) with electron capture detection (ECD). The GC assay of human plasma exhibited a concentration range of 1-20.0 ng/ml. The concentrations of miconazole were calculated from standard curves plotting log-transformed peak-area ratios (miconazole/internal standard) against log-transformed miconazole concentrations.

Limit of Detection: 1 ng/ml

Recovery: Between 50 and 75%

Accuracy: %CV between assays ranged from 2.1-9.6%

#### *Reviewer's Comment*

*The accuracy of the assay is determined from only two runs. No information is provided regarding stability of miconazole nitrate in freeze thaw cycles during assay.*

#### **V. Pharmacokinetic Studies**

The sponsor has conducted one study (# 12966.37C) in infants to evaluate percutaneous absorption of topical miconazole nitrate. Other information on the pharmacokinetics of miconazole nitrate is based on earlier research done by Janssen Research, Belgium or based on literature references and has been summarized in the following sections of this review.

#### **In Vivo Studies**

##### **Absorption**

##### **A. Pediatric percutaneous absorption (Study # 12966.37C)**

This was an uncontrolled, open-label, non-crossover clinical pharmacology study to determine the amount of miconazole absorbed through the skin of infants with diaper dermatitis. A total of 24 infants with moderate-to-severe dermatitis who had been hospitalized for treatment of systemic pathology (primarily gastroenteritis) were enrolled in the study. These subjects aged in the range of 1-12 months. 19 of them (10F and 9M)

received the test medication. There were 10 subjects between ages 1-6 months and 9 subjects between ages 7-12 months. In Mexico, standard treatment of diaper dermatitis with suspected *Candida* infection includes the use of 2% miconazole nitrate cream, therefore, at the discretion of the investigator, additional 5 infants were treated with 2% miconazole nitrate cream.

Test medication was applied to the clinically affected area at each diaper change for 7 days even if the symptoms of diaper dermatitis were no longer visible. Clinical evaluations were conducted at baseline (Day 0/1) and on Days 3, 5, and 7. Blood samples were taken prior to treatment on Day 1 and on Day 7 to determine absorption of miconazole.

### *Results*

The results indicate that the plasma concentrations of miconazole were nondetectable in 15/18 infants and < 5 ng/ml in three others. In 4/5 infants treated with multiple daily applications of 2% miconazole nitrate cream had miconazole concentrations ranging from 5.2 to 7.4 ng/ml and was below the LOD in one subject. The concentrations in the 7 subjects showing detectable levels are attached in the Appendix on page 10.

### *Reviewer's Comment*

*Day 7 may not reflect the highest concentration of miconazole in the infants, because the test medication was to be applied for 7 days even if the symptoms of diaper dermatitis were no longer visible. However, due to the study population being infants, it would not be desirable to take more samples.*

### **B. Percutaneous absorption in adults (referenced from literature<sup>1</sup>)**

The absorption of miconazole from various topical formulations in adults is minimal. Cumulative radioactivity in the urine averaged 0.35% of the applied dose when 1g of cream containing 2% of <sup>3</sup>H-miconazole (20 mg miconazole/subject) was applied under occlusive dressing to the volar side of forearm of male volunteers. Plasma concentration of total radioactivity never exceeded 0.013% ng (~ 2.6 ng equiv/ml) of the 20 mg administered. A similar study conducted by Janssen Research in Belgium in 1978 showed that plasma concentrations of miconazole remained in the range of ≤ 10 ng/ml in 5 male subjects who had received 5 gms containing 100 mg of miconazole as an alcoholic solution or as an oil/water suspension.

### **C. Intravaginal absorption**

The absorption of miconazole through the mucous membrane of the vagina was examined in a series of studies using escalating doses. The absorption was minimal and did not increase linearly with doses of 100, 200 and 1200 mg/subject.

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<sup>1</sup> Brugmans J. et al. Systemic antifungal potential, safety, biotransport and transformation of miconazole nitrate, Eur. J. Clin. Pharmacol. 5, 93-99 (1972)

In a recent study conducted by Johnson & Johnson Advanced Care Products (Clinical Protocol # 95-009-P) plasma concentrations of miconazole nitrate were assessed after intravaginal application of several formulations, including a new formulation containing 4% miconazole nitrate (400 mg/subject/day for three days). The treatment groups studied were:

MONISTAT® 7 vaginal cream (2%), 100 mg dose (once daily for 7 days)

MONISTAT® 7 New formulation (2%), 100 mg dose (once daily for 7 days)

New formulation (4%), 200 mg dose (once daily for 3 days)

The table attached in the Appendix on page 11 shows that the plasma concentrations remained at approximately 10 ng/ml, despite the 12-fold range in administered dose.

The systemic absorption of miconazole was also studied after a single 1200 mg intravaginal dose<sup>2</sup>. The mean peak miconazole concentration was 10.4 ng/ml with a mean AUC value of 967 ng.hr/mL. The mean systemic bioavailability was 1.4%.

#### **D. Other pharmacokinetic information on absorption of miconazole (from literature)**

##### ***Intravenous***

After intravenous administration of 522 mg miconazole, the mean concentration of 6.18 µg/mL was obtained at 15 minutes post infusion. Concentrations of 1.90 and 0.44 µg/mL were obtained at 1 and 4 hours post infusion<sup>3</sup>. Intravenous miconazole has been used in children of all ages, including neonates and newborns. The infusion doses in these studies ranged from 5-21 mg/kg. Plasma concentrations ranged from 100-3600 ng/mL. A table summarizing these literature results is attached in the Appendix on page 11.

##### ***Oral***

Miconazole is not well absorbed from the GI tract after oral administration and the bioavailability is calculated to be 27%. Oral doses of 522 and 1000 mg produced mean peak serum concentration of 0.37 and 1.16 µg/mL, respectively, 2 to 4 hours after administration.

#### **Other pharmacokinetic properties of miconazole nitrate based on literature references**

##### **Distribution**

Miconazole is rapidly and extensively distributed after intravenous administration of miconazole to normal adults. The mean apparent volume of distribution was 1474L. In

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<sup>2</sup> Daneshmend TK. Systemic absorption of miconazole from vagina, J Antimicrob. Chemother., 18, 507-511 (1986)

<sup>3</sup> Janssen Research Report, April 1977

patients with renal disease this value is reduced to 809L<sup>5</sup>. Miconazole is approximately 93% bound to serum albumins<sup>4</sup>.

### **Metabolism**

The information on metabolism of miconazole was obtained following oral administration of radiolabeled miconazole to three male volunteers. In phase I, subjects were administered a single 50 mg dose of <sup>3</sup>H-miconazole. In phase I and II, the same subjects after a 6-day washout period were given a dose of 250 mg of <sup>3</sup>H-miconazole plus 750 mg of unlabeled drug on days 2 and 15. On these days, subjects also received 1 gram of unlabeled drug b.i.d. On Days 1, 3-14 and 16-28, 1000 mg of unlabeled drug was administered t.i.d. for phase II and III. Blood was collected for 72 hours, urine for 96 hours and feces up to 6 days after administration of labeled drug.

Miconazole is highly metabolized in man. Four metabolites in addition to parent drug were isolated from human excreta after oral administration to both rats and humans. The proposed metabolic pathway is attached in the Appendix on page 12. In urine, <1% of an oral dose is present as unchanged drug. In feces, about 40% of an oral dose was recoverable as unchanged drug. Unchanged drug accounts for 14-22% of the administered dose after intravenous administration. In both species (rats and humans), miconazole undergoes oxidative N-dealkylation to form a metabolite which has lost the imidazole ring and which is excreted in the urine (7.9%) and feces (17.8%). Sequential O-dealkylation and oxidative N-dealkylation reactions yield 2, 4-dichloromandelic acid, which is excreted in the urine (9.6%) and feces (15.8%). Miconazole nitrate metabolism is unaffected by repeated oral administration<sup>1,5</sup>.

### **Excretion**

The elimination of miconazole has been studied after single and multiple oral doses of <sup>3</sup>H-miconazole nitrate to humans. Approximately 18% of an administered radioactive dose was excreted in the urine, most of it consisted of metabolites and less than 1% was accounted for unchanged miconazole. Approximately 50% or more of the administered dose was recovered in the feces mostly as unchanged drug<sup>1,5</sup>. Elimination of radioactivity after an intravaginal administration of <sup>3</sup>H-miconazole cream (2%) or suppository to nonpregnant female subjects resulted in mean total recovery from the urine and feces of 1.03% and 0.85%, respectively, of the administered dose<sup>6</sup>.

### **In Vitro Study**

An in vitro permeation study was conducted upon request to investigate the release of elemental zinc from the ointment using occluded Franz Cell model and human cadaver

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<sup>4</sup> Daneshmend et.al, Clinical Pharmacokinetics of Systemic Antifungal Drugs, 8: 17-42 (1983)

<sup>5</sup> R 14889/4 Absorption, metabolism and excretion of miconazole nitrate by human volunteers, Janssen Research Report, August 1970:6-22

<sup>6</sup> Abrams LS. et.al Disposition of radioactivity following intravaginal administration of <sup>3</sup>H-miconazole nitrate, Am J. Obstet. Gynecol, 147(8),970-971 (1983)

skin. This study also included a placebo control and tissue control to quantitate the extent of Zn in the receptor medium due to release of endogenous Zn found in tissues.

The formulations used were:

Placebo, F8705-113, 0.25% miconazole nitrate, 0% ZnO

Test, F8705-053 B3P8-029, 0.25%v miconazole nitrate, 15% ZnO

Dose: 20-40 mg; Thickness of dose 0.40mm; replicates: 6; sampling times 8 and 24 hours, human cadaver average thickness: 0.7039 mm  $\pm$  0.146 mm.

All samples of zinc were analyzed using atomic absorption spectroscopy. The limit of quantitation was 0.05 PPM ( $\mu\text{g/ml}$ ).

The cumulative amount of zinc (mean\*  $\pm$  SD,  $\mu\text{g/cm}^2$ ) in the receptor solution at 8 hours and 24 hours in the control skin, placebo and the test formulation are tabulated below.

Time	Cadaver Skin $\mu\text{g/cm}^2$	0.25% miconazole nitrate, 0% ZnO $\mu\text{g/cm}^2$	0.25% miconazole nitrate, 15% ZnO $\mu\text{g/cm}^2$
8 hours	1.4649 $\pm$ 1.18	0.1677 $\pm$ 0.41	0.7180 $\pm$ 0.93
24 hours**	1.3370 $\pm$ 1.31	0.3892 $\pm$ 0.71	0.8181 $\pm$ 1.15

\*means and SDs are calculated using 0 as zinc concentration when measured zinc concentrations were below the LOQ

\*\*cumulative amount at 24 hours is the combined amount of 8 hours and 24 hours.

The cumulative amounts of zinc in the receptor solution at 8 hours and 24 hours are less than the amount measured for the skin control. Therefore, this data demonstrates that the test composition containing zinc oxide does not deliver measurable amounts of zinc to the receptor solution in this in vitro permeation model.

*Reviewer's Comment (not for the sponsor)*

*This in vitro release study was conducted in order to fulfill the in vivo/in vitro bioavailability requirements for all active ingredients in a dosage form. The study demonstrates very low amounts of zinc release in the receptor solution. However, the study design has a couple flaws. Firstly, the skin should usually be microtomed to a thickness of 0.2 mm. The sponsor has used a cadaver skin that has a thickness of about 0.7 mm. Secondly, cadaver skin from only one donor has been used. Individual variations can be significant, but this can become apparent only when different skin sources are used. These deficiencies are not very critical to this particular study because the proposed OTC monograph (not final yet) allows for the use of 25-40% of zinc oxide.*

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**VI. Conclusions**

Blood concentrations after topical use are at least 50 to 450-fold lower than the range of maximal blood concentrations of 400-3600 ng/ml reported in children administered 7-10 mg/kg intravenously<sup>7</sup>.

Veneeta Tandon 4/21/99

Veneeta Tandon, Ph.D.  
Pharmacokineticist  
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm. D. S. Lee for - 4/21/99

CC: NDA 21-026  
HFD-540/Div File  
HFD-540/CSO/Wright  
HFD-880(Bashaw/Tandon)  
HFD-880(Lazor)  
HFD-344(Viswanathan)  
CDR ATTN: B.Murphy  
HFD-540/Walker  
HFD-540/KO  
HFD-540/Nostrand  
HFD-540/Jacobs

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<sup>7</sup> Lewi Pj. et.al. Pharmacokinetic profile of intravenous miconazole in man, Eur. J. Clin. Pharmacol. 10, 49-54 (1976).

**NDA 21-026  
APPENDIX**

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Table 6. Miconazole Blood Plasma Concentrations > 1 ng/mL in Infants Following Multiple Daily Topical Applications of Miconazole Nitrate

<u>Subject No.</u>	<u>Initials</u>	<u>Age (Months)</u>	<u>Gender</u>	<u>Formulation Concentration</u>	<u>Miconazole Concentration (ng/mL)</u>
11		11	F	0.25%	3.0
16		3.6	F	0.25%	3.5
23	1	2	M	0.25%	3.8
5		10	F	2%	6.8
14		1	M	2%	7.4
17		5	M	2%	5.2
22		10	M	2%	6.6

Reference No. 5 (Study No.12966.37C)

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Treatment Group	Dose <sup>a</sup>	Miconazole Nitrate Concentration (ng/mL) <sup>b</sup>							AUC (ng/h/L)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hours)
		Hours Post Initial Dose									
		0	2	4	8	12	16	24			
Miconazole nitrate (4%) Cream	200	BLQ	0.876 (1.017)	2.501 (2.266)	7.102 (2.747)	8.619 (2.437)	7.644 (3.570)	4.510 (2.851)	136.04 (45.75)	9.490 (2.922)	12.286 (2.920)
MONISTAT®-7 vaginal cream (2% - new base)	100	BLQ	0.616 (0.518)	2.166 (1.554)	5.714 (1.836)	6.410 (2.712)	4.381 (1.982)	2.230 (1.233)	91.43 (35.35)	6.812 (2.363)	10.571 (1.989)
MONISTAT®-7 Vaginal cream (2%)	100	BLQ	0.207 (0.283)	1.029 (0.685)	1.796 (0.484)	1.904 (0.463)	1.621 (0.489)	1.016 (0.414)	32.09 (8.302)	1.993 (0.460)	12.286 (4.286)

Reference Number 13 (Study No. ACP 95009-P)  
<sup>a</sup> (± S.D)

Age	Weight (kg)	Dose Per Infusion <sup>a</sup> (mg/kg)	Miconazole Blood Concentration		Total Daily Dose (mg/kg/day)	Ref
			Time post infusion	Concentration (ng/mL)		
Neonate	0.89	5	1	1600	10	17
Infant 21 Days	0.71	3.8	2	530	11.4	18
			6	190		
			6	270		
Infant 38 Days	4.87	6	2	650	18	18
			6	180		
Infant 35 Days	1.2	4.0	0 <sup>b</sup>	200		19
			0.5	400		
			2	200		
			0 <sup>c</sup>	100		
			0.5	400		
8 Months	19	10.5	1	3600	32-63	20
			7	2000		
			7	810		
16 months	36	11.1	1	5000	17-33	20
1.5 Years	9.5	8.9	1	1600	27	20
			7	250		
2.5 Years	12	16.6	7	400	50-60	20

<sup>a</sup> Infusion times varied from 15 mins. to 8 hrs.  
<sup>b</sup> After six days treatment  
<sup>c</sup> After two days treatment

1 Page(s) Withheld

2 Trade Secret / Confidential

       Draft Labeling

       Deliberative Process

45 DAY MEETING CHECKLIST OCT 13

FILEABILITY:

On initial overview of the NDA application:

YES

NO

BIOPHARMACEUTICAL:

(1) On its face, is the biopharmaceutics section of the NDA organized in a manner to allow substantive review to begin? ✓

(2) Is the biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin? ✓

(3) On its face, is the biopharmaceutics section of the NDA legible so that substantive review can begin? ✓

(4) Are the Phase 1 studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? ✓

(5) If several formulations of the product were used in the clinical development of the product, has the sponsor submitted biopharmaceutics data to allow comparison between the product to be marketed and the product(s) used in the clinical development? w/ reservation

(6) From a biopharmaceutic perspective, is the NDA fileable? If "no", please state below why it is not? w/ reservation

*Sponsor has not addressed issue of zinc oxide absorption (see attached review). The sponsor was told to address this issue at the pre-NDA mtg. Given the extensive literature of zinc oxide it may be possible to address this issue from the literature. This issue should be brought to the attention of the sponsor ASAP.*

\_\_\_\_\_  
Reviewing Biopharmaceutics Officer

*E. Donald Paul*  
\_\_\_\_\_  
Supervisory Biopharmaceutics Officer 10/13/98

## Clinical Pharmacology/Biopharmaceutics Review

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NDA: 21-026

SUBMISSION DATE: 8/24/98

PRODUCT: Pediastat™ Diaper Rash Ointment  
(Miconazole nitrate 0.25%)

SPONSOR: Johnson & Johnson  
Skillman, NJ 08558

REVIEWER: Veneeta Tandon, Ph.D.

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### NDA Filing Memo

Pediastat™ Diaper Rash Ointment contains synthetic antifungal agent, miconazole nitrate (0.25%) in a zinc oxide (15%) and petrolatum base for dermatologic use. It is indicated in the treatment of moderate to severe diaper dermatitis where *Candida albicans* may be a contributing factor.

The topical absorption of 0.25% miconazole nitrate ointment was studied in male and female infants with diaper dermatitis ranging in age from one month to 12 months. After multiple applications for seven days, the plasma concentrations of miconazole were nondetectable (< 1 ng/ml) in 15/18 of the patients and 3-3.8 ng/ml in other studies. In the same study five infants were treated with multiple daily applications of 2% miconazole nitrate cream, showed blood concentrations ranging from 5.2 to 7.4 ng/ml. One subject was below the limit of detection.

The sponsor has also submitted literature reports of plasma miconazole concentrations after intravenous administration in pediatrics and after oral, topical, intravaginal and intravenous administration in adults. The summary of all the results is attached on the following page.

Blood concentrations after topical administration are at least 50-450-fold lower than the range of maximal blood concentrations of 400-3600 ng/ml reported in children administered 7-10 mg/kg intravenously.

### Recommendation

Systemic exposure of miconazole following topical administration has been demonstrated in patients (infants). However, there has been no assessment of the bioavailability of zinc oxide. The applicant claims that is a vehicle in the formulation of the ointment, but at strength of 15% zinc oxide could also act as a skin protectant. Zinc oxide will not be active against *Candida albicans*, however, may have therapeutic effect in the treatment of diaper rash in infants. It is not easy to evaluate the in vivo zinc oxide concentrations after topical application of the ointment, therefore, the applicant should by in vitro methods demonstrate the release of zinc oxide from the ointment base. The application could be

fileable from the biopharmaceutics standpoint upon availability of data demonstrating the release pattern of zinc oxide.

*Veneeta Tandon 9/17/98*

Veneeta Tandon, Ph.D.  
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Team Leader: E. Dennis Bashaw, Pharm. D. *Ed 9/18/98*

CC: NDA 21-026  
HFD-540/Div File  
HFD-540/CSO/Wright  
HFD-880(Bashaw/Tandon)  
HFD-880(Lazor)  
HFD-344(Viswanathan)  
CDR ATTN: B.Murphy

CM

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