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RESEARCH**

*APPLICATION NUMBER:*

**21-026**

**MICROBIOLOGY REVIEW(S)**

DIVISION OF ANTIINFECTIVE DRUG PRODUCTS (HFD-520)  
CLINICAL MICROBIOLOGY REVIEW  
CONSULT FROM DIVISION OF DERMATOLOGY/DENTAL DRUG PRODUCTS  
(HFD-540)

NDA 21-026

Review completed: 6 May 05

Date company submitted: 24 Nov 04  
Date received from HFD-540: 6 Dec 04  
Reviewer: Fred Marsik, Ph.D.

Date received by CDER: 24 Nov 04  
Date assigned: 6 Dec 04

**NAME AND ADDRESS OF APPLICANT**

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Note: The sponsor of this NDA originally was Johnson and Johnson Consumer Products Worldwide

**CONTACT PERSON**

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**DRUG PRODUCT NAME**

Proprietary: ZIMYCAN™  
Established name: Miconazole nitrate  
Chemical name, formulae, and molecular weight: See USP: Miconazole nitrate"

**PROPOSED PEDIATRIC INDICATION**

Treatment of diaper dermatitis complicated by candidiasis

**DOSAGE FORM, STRENGTH, ROUTE OF ADMINISTRATION AND DURATION OF TREATMENT**

Dosage form: Ointment  
Strength: 0.25%  
Route of administration: Topical  
Dosage, administration and duration: Ointment is to be applied to the entire affected area at each diaper change. Before applying the ointment, cleanse the skin with lukewarm water. Treatment is to be continued

**DISPENSED**

Rx

b(4)

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CONSULT FROM DIVISION OF DERMATOLOGY/DENTAL DRUG PRODUCTS  
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**RELATED DOCUMENTS**

b(4)

21-542,  
18-520

NDA 17-450, NDA 17-494, NDA 18-040, NDA

**REMARKS**

This NDA was the subject of a non-approvable letter dated July 24, 2000. Barrier Therapeutics assumed ownership of the product from Johnson and Johnson Consumer Products Worldwide after the issuance of the non-approvable letter. In this submission Barrier Therapeutics submits an amendment to NDA-21-026 to respond to the deficiency cited in the Agency's "not approvable" letter.

The primary deficiency in order for the application to be approved by the Agency was that an adequate and well-controlled clinical trial needed to be conducted in which the severity of the diaper dermatitis was to be adequately defined and the involvement of *Candida albicans* was to be proven. Barrier Therapeutics conducted a Phase 3, randomized, double-blinded, vehicle controlled clinical study, BT100USA/001 which they consider to be the pivotal clinical study the Agency requested.

**CONCLUSION**

The results of study BT100USA and data from other studies provided by the Applicant in this submission suggest that 0.25% miconazole nitrate may play some role in the treatment of diaper dermatitis. Data from clinical trial BT100USA provided no evidence that treatment failure in the 0.25% miconazole treatment group was the result of *C. albicans* developing resistance to miconazole nitrate.

**LABELING**

**SPONSOR'S PROPOSED LABEL**

The sponsor is proposing the microbiology statement in the following under pharmacology (Vol. 21, pg. 4).

**CLINICAL PHARMACOLOGY**

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AGENCY'S PROPOSED LABELING

Microbiology: The miconazole nitrate component on this product has been shown to have in vitro activity against *Candida albicans*, an organism that is associated with diaper dermatitis. The activity of miconazole nitrate against *C. albicans* is based on the inhibition of the ergosterol biosynthesis in the cell membrane. The accumulation of ergosterol precursors and toxic peroxides results in cytolysis. *Candida albicans* resistance to miconazole nitrate is unusual. The clinical significance of the in vitro activity of miconazole nitrate against *C. albicans* in the setting of diaper dermatitis is unclear.

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**INTRODUCTION**

Epidemiology Studies (Published literature)

A literature search for "*Candida albicans*" and "diaper rash" was conducted using PubMed software at National Library of Medicine. A search of the literature produced some papers published within the last several years dealing with the current thoughts on the prevention, and diagnosis of diaper dermatitis. A few recent papers were found on the development of resistance to miconazole among yeast organisms. No papers were found in relation to the development of resistance to miconazole when it is used for the treatment of diaper dermatitis.

Overview of the Etiology of Diaper Dermatitis

Microbial factors have long been viewed as important etiological factors in diaper dermatitis (1-4). A variety of organisms, including *Staphylococcus aureus*, and Gram-negative organisms (e.g. *Escherichia coli* and *Proteus* spp.) have been recovered from inflamed rash areas (5). *Candida albicans* is implicated in the maintenance or worsening of the condition (5-7). In conditions of warmth and moisture, as under an occlusive diaper, *Candida albicans* can proliferate on the skin surface and then penetrate the stratum corneum to induce inflammation (7-11). Furthermore, low numbers of *Candida albicans* are capable of inducing dermatitis (5, 12). The dermatitis produced by *Candida albicans* is typically erythematous papules or vesicles involving the inguinal folds as well as the genitals, buttocks, and inner thighs. While *Candida albicans* is not routinely found on normal skin, it is present in the gastrointestinal tract, and it is presumably introduced via the feces (9). Reports on the presence of *Candida* vary. Recovery of the organism in up to 77% of subjects with diaper dermatitis has been reported (13).

Diagnosis of the Etiologic Agent of Diaper Dermatitis

The literature is ambiguous as to what the most common approach among physicians is to diagnosing the etiologic agent that may be causing diaper dermatitis when an infant is first seen with the condition. Some literature supports the use of a KOH (potassium hydroxide) wet mount looking for the presence of yeast organisms or culture of the infected site for the presence of yeast organisms because the differential diagnosis includes other eruptions that may coexist with *Candida* infection (14, 15). Other literature supports recognition of the entity by characteristics of its dermatological manifestations (16, 17).

**IN VITRO STUDIES**

Antimicrobial Spectrum of Activity

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The Applicant has not provided, in this submission, any new data on the in vitro susceptibility of *Candida albicans* isolates to miconazole nitrate. The data they have provided in this submission was provided in the original NDA submitted by Johnson and Johnson August 24, 1998.

It should be noted that the interpretation of the in vitro susceptibility data below is difficult because much of the data is based on non-standardized susceptibility testing methods.

From 1980 to 1986 a total of 2602 isolates belonging to 107 fungal species, 5 species of *Actinomycetales* and one alga were tested for sensitivity to miconazole nitrate by Janssen Pharmaceutica NV (18). Of the 2602 isolates tested, 1740 (Table 1) were isolates of the five species most commonly associated with vaginal candidiasis. 1328 isolates of *Candida albicans*, 76 isolates of *Candida tropicalis*, 74 isolates of *Candida parapsilosis*, 45 strains of *Candida krusei* and 217 strains of *Candida (Torulopsis) glabrata* were evaluated to determine the concentration of miconazole nitrate necessary to completely inhibit development of the organisms. Results with these organisms are listed in Table 1.

Growth of most isolates was inhibited at miconazole nitrate concentrations of 10 µg/mL or lower. In the case of *Candida albicans*, 67% of the isolates were inhibited at miconazole nitrate concentrations of 0.01 to 1.0 µg/mL. Only one isolate of *Candida albicans* was not inhibited at a miconazole nitrate concentration of 100 µg/mL. The frequency of more resistant MICs is low among these historical data from a large number of isolates. Only 2 of 1740 isolates (0.12%) required a miconazole nitrate concentration of 100 µg/mL to inhibit growth.

Table 1

Antimicrobial Activity of Miconazole Nitrate

Species	# strains Tested	Number of strains inhibited at miconazole nitrate concentration (µg/mL)					
		0.01	0.1	1.0	10	100	>100
<i>C. albicans</i>	1328	52	155	678	441	1	1
<i>C. tropicalis</i>	76	0	12	37	27	0	0
<i>C. parapsilosis</i>	74	0	21	39	14	0	0
<i>C. krusei</i>	45	1	5	19	20	0	0
<i>C. glabrata</i>	217	2	8	163	43	1	0

A compilation of the MIC ranges for a variety of *Candida* species to miconazole is given below in Table 2 (19).

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Table 2

MIC Ranges for Miconazole Against a Variety of *Candida* species

<u>Organism (number of isolates)</u>	<u>MIC (<math>\mu\text{g/mL}</math>) range</u>
<i>Candida albicans</i> (1815)	0.016 – 100
<i>Candida glabrata</i> (224)	0.016 – 64
<i>Candida krusei</i> (40)	<0.063 – 6.25
<i>Candida parasilopsis</i> (54)	0.016 – 32
<i>Candida tropicalis</i> (172)	0.16 - 32

In 1982, Johnson & Johnson Baby Products Company did a study to determine the effect of zinc oxide in the formulation on miconazole nitrate (20). A test was run in vitro against *Staphylococcus aureus* and *Candida albicans*. The study showed that a combination of miconazole and zinc oxide in this test system exhibited a synergistic effect in the ability to inhibit growth of *S. aureus*. When tested with *Candida albicans*, low concentrations of the zinc oxide decreased the efficacy of miconazole nitrate, while higher concentrations showed a synergistic effect.

#### Mechanism of Action

The mode of action of imidazole derivatives has been investigated at the biochemical as well as the morphological level (21-27). The activity of miconazole is based on the inhibition of the ergosterol biosynthesis in the cell membrane of the microorganism. The major effects of imidazoles and triazoles on fungi are inhibition of sterol 14- $\alpha$ -demethylase, a microsomal cytochrome P-450-dependent enzyme system. Imidazoles and triazoles impair the biosynthesis of ergosterol for the cytoplasmic membrane and lead to the accumulation of 14- $\alpha$ -methylsterols. The accumulation of ergosterol precursors and toxic peroxides results in cytolysis (2, 28).

*Candida albicans* cells have been observed to exhibit progressive cytoplasmic deterioration and permanent shape changes resulting in complete cell necrosis depending on the dose and duration of exposure to miconazole nitrate (29-31). Early studies of miconazole nitrate showed that this agent affects the permeability of the cell membrane of sensitive cells (21-23). Cell membrane effects are evidenced by leakage of potassium ions and phosphorus containing compounds. Low fungistatic concentrations of miconazole nitrate inhibit the uptake of purines and glutamine by *C. albicans* (21). These changes in the cell membrane are consequences of interference with biosynthesis of lipids

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in the fungal cell, especially with the synthesis of sterols (12, 27). Sterols are components of many biological membranes, and an alteration in the amount and composition of sterols in newly formed membranes affects cellular structure and function. Ergosterol is the main sterol of fungal cell membranes. Van den Bossche and his associates (26, 27) have shown that low concentrations of miconazole nitrate inhibit the incorporation of [<sup>14</sup>C] acetate into ergosterol in *C. albicans*. This inhibition coincides with an accumulation of lanosterol-like sterols, i.e., sterols with a 14- $\alpha$ -methyl group in their structure. The accumulation of C14-methylsterols suggests that miconazole nitrate is a potent inhibitor of one of the metabolic steps involved in the demethylation at the C14 site. The faulty membranes produced from such action lead to inhibition, usually manifested as a modest but significant reduction in growth rate. At concentrations greater than  $10^{-5}$  mol ( $\sim 4$   $\mu$ g/mL), miconazole nitrate exerts direct physiochemical cell damage against *Candida albicans* evident as a rapid and pronounced lethal action (28, 29).

Miconazole nitrate has been shown to have an effect on oxidative and peroxidative enzymes (31, 32). Fungi possess a series of oxidative enzymes that are required for respiratory and metabolic functions including cytochrome C oxidase and nicotinamide adenine dinucleotide [reduced form]- (NADH-) dependent oxidase. Oxidative pathways lead to the production of hydrogen peroxide, which, if not broken down, is toxic to the cell. The normal cell, therefore also possesses cytochrome C peroxidase and catalase, two enzymes that break down peroxide and thus maintain cell viability. Treatment with low concentrations of miconazole nitrate results in production of greater amounts of peroxide as the consequence of increased NADH-dependent oxidase activity. Simultaneously, the activity of peroxidase is suppressed and that of catalase is enhanced. With fungicidal doses of miconazole nitrate, NADH-dependent hydrogen peroxide production continues, whereas the activity of both peroxidase and catalase is totally inhibited. The intracellular buildup of hydrogen peroxide in toxic concentrations may contribute to the observed degeneration of subcellular structures that precedes cell death.

Typically, the published work pertaining to structural changes after imidazole treatment has involved yeast-phase cells of *C. albicans* (33-35). The effects of low levels of miconazole nitrate on morphology are similar and primarily involve alterations of the cell membrane, changes in cell volume and defective cell division. Deposition of abnormal membranous elements near the cell wall is characteristic of cells treated with a low dose (0.05  $\mu$ g/mL) and is probably the morphologic translation of the effects on lipid biosyntheses.

Involution of internal organelles of fungal cells occurs after exposure to higher fungistatic concentrations of miconazole nitrate; the central vacuole becomes enlarged and the number of peroxisomes increases. The cells become angular in shape, most probably as an expression of the loss of osmotic resistance. Necrotic changes involving the great majority of cells are seen in the presence of fungicidal concentrations of miconazole

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nitrate (5-50 µg/mL) (35, 36).

The imidazole group of miconazole is subject to protonation (pKa approximately 6.5). Studies have suggested that the direct lethal effect of miconazole against *C. albicans* require nonprotonated drug molecules. Viability studies have suggested that the direct lethal effect of miconazole is inhibited with increasing as well as decreasing pH (i.e., pH <6.0 and >7.0) (37).

#### Mechanism(s) of Resistance

Resistance to the azole antimicrobials occurs because: 1) there is a modification in the quality or quantity of the enzyme associated with the production of ergosterol, 2) there is reduced access to the target enzyme, and 3) there is a combination of 1 and 2. As of yet there are no reports of modification of azole antimicrobials by the target microorganism as a mechanism of resistance (22).

There have been no well-controlled studies addressing the issue of resistance developing to miconazole when it is used to treat diaper dermatitis. Neither have there been reports in the literature suggesting that such use has brought about diaper dermatitis cause by *C. albicans* that is refractory to treatment with miconazole. The development of *C. albicans* resistant to the azole class of antifungals has been reported when used in the treatment modality of patients with *Candida* vulvovaginitis, cancer patients and AIDS patients (38).

Development of resistance to miconazole nitrate is infrequent. It has been difficult to isolate resistant mutants of *Candida albicans* in the laboratory (39, 40). In one laboratory study, no mutant with significantly greater resistance to miconazole nitrate could be induced to appear following repeated passages on gradient plates (39). However, these laboratory experiments carry with them the uncertainties of conclusions associated with any negative mutant hunt.

The prime concern about resistance to miconazole nitrate has been most extensively viewed as a potential cause in the etiology of recurrent vulvovaginal candidiasis. To adequately address the role of antifungal resistance as a potential mechanism for this condition, a longitudinal susceptibility analysis of 177 *C. albicans* isolates collected from 50 *C. albicans* patients over a period of 3 months to 7 years was performed (41). Antifungals tested included miconazole, clotrimazole, ketoconazole, itraconazole and fluconazole. Results of in vitro susceptibilities of multiple *C. albicans* isolates convincingly showed that numerous isolates collected for up to 7 years from women with recurrent vulvovaginal candidiasis were equally sensitive to all antifungals tested by the current NCCLS reference method (42) for susceptibility testing of yeasts. Successive isolates from individual patients did not show increased resistance to any drug despite long-term exposure to azoles. Additionally, there was no increase in minimal inhibitory concentrations (MICs) as a result of prolonged therapy, and the MICs from the majority

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of longitudinal isolates collected from individual women did not shift with any drug over time. These results suggest that episodes of recurrent vulvovaginal candidiasis caused by *C. albicans* are attributable to mycological failure to respond to therapy rather than development of in vitro resistance to azole antifungals. Although development of resistance was not observed in this study, the products labeled for vulvovaginal candidiasis have a much higher content of miconazole (2%) (43). These vulvovaginal studies may not be applicable to predicting emergence of resistance of *Candida* to miconazole for the product, which is the subject of this application, due to its reduced content of miconazole.

In a recent study, Boschman and associates (38) looked at 13-year evolution of azole resistance in yeast isolates from cancer patients at a large medical center. The azoles studied included fluconazole, ketoconazole, itraconazole and miconazole. From 1984 to 1992 all of the yeast isolates tested was susceptible to fluconazole, ketoconazole, and miconazole. Itraconazole was not introduced for use until 1996. During the years 1994, 1995, 1996, and 1997 83%, 84%, 97% and 97% of yeast isolates remained susceptible to miconazole. A similar percentage of strains for fluconazole, ketoconazole, and itraconazole remained susceptible to these antifungals.

Two studies (44, 45), closer to the Applicant's request for the use of miconazole were found and reviewed. One study (44) compared the effectiveness of over-the-counter products containing 2% miconazole nitrate to inhibit the growth of *C. albicans*. The author's conclusions were that the over-the-counter products were as effective as mycostatin cream in inhibiting the growth of *C. albicans* and that the 2% miconazole nitrate was also inhibitory to *C. albicans* at greater dilutions than five other antifungal products containing chloroxylenol and clotrimazole. The other study (45) evaluated the use of a miconazole containing paste in the treatment of diaper dermatitis. The authors concluded that miconazole-nitrate-containing paste where the concentration of miconazole is a 2% reduces the erythema and corneum alterations of the skin and provides the diapered skin with an improved microbial environment. Neither reference 44 or 45 mentions miconazole resistant *C. albicans*.

In a paper published in 1987 (46) Beggs noted that miconazole at concentrations  $>10^{-5}$  mol can induce direct physicochemical damage to late lag and early to mid logarithmic phase yeast cells of *C. albicans*. As stationary phase is approached, however, susceptibility to this direct-lethal action (DLA) is lost and early to mid stationary phase cells are quite resistant to being killed (46). In a later paper by Beggs et al (47) it was demonstrated that miconazole at a sub-level-DLA of  $2.0 \times 10^{-6}$  mol ( $\sim 0.8 \mu\text{g/mL}$ ) reverted *C. albicans* cells in early logarithmic phase (DLA-susceptible) to DLA resistant. In a more recent study (48) Beggs suggests from experimental evidence that in the presence of a sub-level-DLA concentration of miconazole that important alterations in existing membrane material and not extensive incorporation of faulty components into newly synthesized membranes occurs. Beggs proposes that without the proper building

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components faulty membrane is produced, resulting in impaired growth. Coincidentally, these faulty membranes lack chemical components and structural configurations required for DLA of miconazole.

Recent research has shown that resistance to antifungals in *C. albicans* having to do with efflux is mediated by certain genes (22). To date there seem to be two general gene groups mediated resistance by efflux. These groups are referred to as the MFS (major facilitator superfamily and the ABC (ATP-binding cassette) superfamily of proteins (22). To date, eight genes for ABC transporters have been identified in *Candida*. An example of such a gene is CDR1 (*Candida* drug resistance gene), which is involved in resistance to azoles (22). Researchers have shown that transient expression of this gene occurs when there is exposure to miconazole (49).

## IN VIVO STUDIES

### HUMAN AND ANIMAL STUDIES

#### Pharmacokinetics/Bioavailability

The site of microbiological activity for this drug product is on the skin surface, epidermis and dermis, correlating to the site of the *Candida* infection. The pharmacokinetic profile of miconazole nitrate is not provided in this application.

#### Animal Prophylactic and Therapeutic Studies

The effectiveness of miconazole nitrate has been demonstrated in several experimental animal models. Van Cutsem and Thienpont (50) demonstrated the efficacy of miconazole nitrate given orally or topically against cutaneous infections with *Candida albicans*, *Trichophyton mentagrophytes*, and *Microsporium canis* in guinea pigs. In another study, all mice given miconazole base intramuscularly and subcutaneously 4 days after infection with 50 or 100% lethal doses of *Coccidicoides immitis* were protected, whereas 60 to 100% of the untreated mice succumbed (51). Cultural assays of lung tissue confirmed that the drug limited proliferation of the fungus at that site. Miconazole nitrate, at concentrations of 1.0 and 2.0%, was shown to be effective in the topical treatment of experimentally induced *Candida* keratitis. The drug proved effective in reducing inflammation and producing mycological cures in these developmental animal model experiments (52).

### CLINICAL STUDIES

#### Clinical Study BT100USA/001

In response to the non-approvable letter issued by the Agency July 24, 2000 noting that

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the primary deficiency of the application was the lack of a well controlled clinical trial. Barrier Therapeutics conducted a Phase 3, randomized, double-blind, vehicle controlled clinical study, BT100USA/001.

Study BT100 USA/001 was designed to evaluate the efficacy of 0.25% Miconazole nitrate ointment in the treatment of diaper dermatitis where *Candida albicans* involvement was proven, and therefore only enrolled subjects with a positive KOH and culture results for *Candida* spp. at the baseline visit. Evaluations in Study BT100 USA/001 included cultures for *Candida* spp. at Baseline (Day 0), Day 7 and an additional test-of-cure at Day 14. The applicant feels that study BT100 USA/001 was unique in that the day 14 visit was designed specifically to evaluate the efficacy of the formulation through the evaluation of clinical cure and microbiological eradication of the pathogen *Candida* spp.

#### Methodology

This clinical study was conducted as a randomized (1:1), double-blind, vehicle-controlled, multi-center trial. The study was conducted at 20 investigational sites in the United States and Latin America. Subjects were randomized to treatment with either 0.25% miconazole nitrate ointment (Formula No. F114), or the vehicle control (Formula No. 116). The test medication was applied to all clinically affected areas of diaper dermatitis at each diaper change (approximately 5 to 10 times per day) for seven days, whether or not symptoms remained present. The duration of treatment was seven days. Clinical evaluations were performed on Days 0, 3, 5 (optional), 7 and 14; cultures for the presence of *Candida* spp. were obtained at the baseline visit, end-of treatment (day 7), and at the test of cure (day 14). Subjects who were negative for the presence of *Candida* spp. at baseline were excluded from the efficacy analyses, but included in the safety analyses.

The primary efficacy evaluation was therapeutic response at the test-of-cure, which required that subjects were assessed as both clinically cured and the *Candida* spp. eradicated. Clinical and microbiological evaluations were performed at the day 14 visit. The secondary efficacy variable was clinical cure as measured by the diaper dermatitis severity index score. Clinical cure was defined as total resolution of all signs and symptoms of the infection (i.e. diaper dermatitis severity index score of 0). If the diaper dermatitis severity index score was greater than 0, then the subject was considered to be a clinical failure and thus a treatment failure. Microbiological eradication was defined as no growth of the pathogen *Candida* spp. at the test-of-cure. Those subjects with growth of the pathogen at the test-of-cure visit, or those who missed this visit, were deemed a microbiologic failure. Any subject for whom the test-of-cure culture result was lost, damaged, or considered not reliable was considered a microbiologic failure.

In addition, a follow-up telephone interview was conducted on Day 28 to determine from the caregiver the condition of the child's diaper dermatitis. A brief questionnaire was

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completed, which inquired as to the child's overall health, new medical history, recurrence of diaper dermatitis, and any new products used.

Diagnosis and criteria for inclusion

Subjects were male and female, with Fitzpatrick Skin Type I to VI who wore commonly available diapers day and night. The protocol specified subjects could be neonates, infants, and children through four years of age; however, enrolled subjects were up to 35 months. Subjects had clinical evidence of diaper dermatitis defined as an overall diaper dermatitis severity index score of 3 to 8 at the baseline visit, including an overall clinical grade of at least 2 for erythema. Subjects also had a positive KOH test result for pseudohyphae and/or budding yeast at baseline. Cultures for the presence of *Candida* spp. were obtained at the baseline visit; subjects having a negative culture result at baseline were excluded from the efficacy analysis.

Results

A total of 330 subjects were enrolled in the study; 166 subjects were treated with the active ointment and 164 treated with the vehicle control. A total of 236 subjects had a positive culture for the presence of *Candida* spp. (112 active, 124 vehicle control) completed the study and were included in the MITT population.

**In vitro susceptibility test results for the *C. albicans* isolates obtained during the clinical trial**

Table 3 shows the MIC findings for *C. albicans* isolates obtained during the clinical trials from both the treatment group and the placebo group after 24 hours incubation. Table 4 shows the results after 48 hours of incubation. The MIC data for the *C. albicans* isolates is consistent with the information in the literature for the miconazole nitrate susceptibility of *C. albicans* (19). As can be seen the MICs for the *C. albicans* did not change dramatically after 48 hours of incubation compared to 24 hour results.

Table 3. MIC findings for *Candida albicans* from ZIMYCAN clinical study after 24 hours incubation

MIC µg/mL	0.25% miconazole nitrate	Vehicle	Composite summary n (%)
	ointment n (%)	control n (%)	
≤0.03	95 (99.9)	100 (98.0)	195 (98.5)
0.06	0	2 (2.0)	2 (1.0)
1	1 (1.0)	0	1 (0.5)
TOTAL	96	102	198

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Median	≤0.03	≤0.03	≤0.03
MIC <sub>50</sub>	≤0.03	≤0.03	≤0.03
MIC <sub>90</sub>	≤0.03	≤0.03	≤0.03

Table 4. MIC findings for *Candida albicans* from ZIMYCAN clinical study after 48 hours incubation

MIC µg/mL	0.25% miconazole nitrate	Vehicle	Composite summary
	ointment	control	
	<u>n (%)</u>	<u>n (%)</u>	<u>n (%)</u>
≤0.03	87 (90.9)	93 (91.2)	180 (90.9)
0.06	8 (8.3)	8 (7.8)	16 (8.1)
0.25	0	1 (1.0)	1 (0.5)
1	1 (1.0)	0	1 (0.5)
TOTAL	96	102	198
Median	≤0.03	≤0.03	≤0.03
MIC <sub>50</sub>	≤0.03	≤0.03	≤0.03
MIC <sub>90</sub>	≤0.03	≤0.03	≤0.03

Specimens were collected from patients that were considered to be clinical failures to determine if *C. albicans* was still present and to determine the miconazole nitrate susceptibility of the isolates that were recovered. Table 4 shows the baseline miconazole nitrate MIC for *C. albicans* isolates after 48 hours of incubation of the susceptibility test plates. Table 5 shows the miconazole nitrate MIC after 48 hours of incubation for the *C. albicans* isolates obtained at the test of cure (14 days). As can be seen the MICs for the isolates of *C. albicans* did not change in any significant way from the baseline MICs for those patients in either the treatment failure group or the placebo treatment group. One patient in the miconazole treatment group and one patient in the placebo treatment group had *C. tropicalis* isolated at baseline and at the test of cure (data not shown). The miconazole nitrate MICs for the *C. tropicalis* isolates (0.03 µg/mL) did not change over the course of treatment. This data provides evidence that treatment failure was not due to development or miconazole resistance.

Table 4. Miconazole nitrate MIC findings for *C. albicans* isolates obtained at baseline after 48 hours of incubation of susceptibility test plate

MIC µg/mL	0.25% Miconazole nitrate ointment	Vehicle control	Composite summary
	<u>Number (%)</u>	<u>Number (%)</u>	<u>Number (%)</u>
≤0.03	30 (83.3)	22 (95.7)	52 (88.1)

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0.06	3 (8.3)	1 (4.4)	4 (6.8)
0.125	1 (2.8)	0 (0.0)	1 (1.7)
0.25	1 (2.8)	0 (0.0)	1 (1.7)
0.5	1 (2.8)	0 (0.0)	1 (1.7)
Total	36	23	59
Median MIC	≤0.03	≤0.03	≤0.03
MIC <sub>50</sub>	≤0.03	≤0.03	≤0.03
~MIC <sub>90</sub>	0.05	≤0.03	0.06

Table 5. Miconazole nitrate MIC findings for *C. albicans* isolates obtained at test of cure (day 14) after 48 hours of incubation of susceptibility test plate

MIC µg/mL	0.25% Miconazole nitrate ointment	Vehicle control	Composite summary
	Number (%)	Number (%)	Number (%)
≤0.03	31 (86.1)	22 (95.7)	52 (88.1)
0.06	31(2.8)	0 (0.0)	4 (6.8)
0.125	1 (2.8)	0 (0.0)	1 (1.7)
0.25	2 (5.6)	1 (4.4)	1 (1.7)
0.5	1 (2.8)	0 (0.0)	1 (1.7)
Total	36	23	59
Median MIC	≤0.03	≤0.03	≤0.03
MIC <sub>50</sub>	≤0.03	≤0.03	≤0.03
~MIC <sub>90</sub>	0.125	≤0.03	0.06

## EFFICACY RESULTS

Table 6 presents clinical and microbiologic evaluations and the therapeutic response (overall cure) at the day 14 test-of-cure visit for the MITT population. Microbiological eradication was reported for 56 subjects (50%) in the 0.25% miconazole nitrate ointment treatment group, compared to 29 subjects (23%) in the vehicle control group. Table 7 presents the clinical, microbiological, and therapeutic response without the presence of "Other *Candida* spp." and without "Missing" mycological cultures.

A therapeutic response was defined by the applicant as a clinical cure (diaper dermatitis severity index of 0) and microbiological eradication (no growth of the pathogen *Candida* spp.). Therapeutic response rates for the subjects using 0.25% miconazole nitrate ointment (Table 6 = 23%, Table 7 = 26%) were more than twice that of the subjects using the vehicle control (10%) at the test-of-cure visit, and the difference was also statistically significant (Table 6: p=0.005, Table 7: p=0.002). However, there were a substantial

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number of failures in the therapeutic response and the clinical response groups. With the miconazole nitrate susceptibility of the *C. albicans* isolated from the subjects being what it was (see Table 3) it is curious that there were not higher success rates (microbiological and clinical) if elimination of *C. albicans* is a key factor in controlling diaper dermatitis. The preparation containing the miconazole nitrate, however, did significantly better than the vehicle control suggesting that the miconazole nitrate may play a role in treating diaper dermatitis. This data supports the fact that there are factors other than the presence of *C. albicans* that cause the diaper dermatitis. The results, however, raise the question as to whether it is necessary to have an antifungal in a preparation for the treatment of diaper dermatitis.

Table 6. Significant differences between treatment groups in clinical and microbiologic evaluations at the day 14 test-of-cure visit (Modified Intent to Treat subjects in Study BT100 USA/001) (Volume 2.2, Attachment 3, pg. 610)

<u>Evaluation Endpoint</u>	<u>Active Treatment</u> <u>(N=112)</u>	<u>Vehicle Control</u> <u>(N=124)</u>	<u>p-</u> <u>Value</u>
<b>Mycological Culture</b>			
Both cultures negative	56 (50%)	29 (23%)	
<i>Candida albicans</i>	39 (35%)	30 (24%)	
Other <i>Candida</i> spp.	3 (3%)	1 (1%)	
Missing	14 (13%)	64 (52%)	
<b>Clinical Response (a)</b>			
Success	43 (38%)	14 (11%)	<0.001
Failure	69 (62%)	110 (89%)	
<b>Microbiologic Response (b)</b>			
Success	56 (50%)	29 (23%)	
Failure	56 (50%)	95 (77%)	
<b>Therapeutic Response (c)</b>			
<b>Overall Cure</b>			
Success	26 (23%)	12 (10%)	0.005
Failure	86 (77%)	112 (90%)	

a. success was defined as clinically cured (total resolution of all signs and symptoms of the infection-diaper dermatitis severity index score of 0)

b. success was defined as microbiologically eradicated (no growth of the pathogen *Candida* spp.)

c. success was defined as clinically cured (total resolution of all signs and symptoms of the infection-diaper dermatitis severity index of 0) and microbiologically eradicated (no growth of the pathogen *Candida* spp.)

P-value from a Cochran-Mantel-Haenzel test, stratified by grouped study center. Cross Reference:

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BT100 USA/001 CSR Tables 11.4.1.3 and 14.2.1.1

Table 6 is a summary of clinical and microbiologic evaluation at the day 14 test-of-cure excluding subjects with missing mycological culture data and other *Candida* spp. (supplemental data provided by Applicant in submission dated 15 Mar 05). Taking out the missing mycological data and other *Candida* spp. did not make a major difference in the various response groups.

Table 7. Clinical and microbiologic evaluations at the day 14 test-of cure visit excluding subjects with missing mycological culture data and other *Candida* spp.

<u>Response</u>	0.25% miconazole nitrate ointment <u>N = 100</u>	Vehicle control <u>N=118</u>	<u>P-value</u>
<b>Clinical</b>			
Success	40 (40%)	14 (12%)	<0.001
Failure	60 (60%)	104 (88%)	
<b>Microbiologic</b>			
Success	56 (56%)	29 (25%)	
Failure	44 (44%)	89 (75%)	
<b>Therapeutic Overall Cure</b>			
Success	26 (26%)	12 (10%)	0.002
Failure	74 (74%)	106 (90%)	

In addition, the difference between the treatments on days 3, 5, 7, and 14 as well as the change from baseline to day 3 in diaper dermatitis severity index scores were all statistically significant for the MITT population ( $p < 0.001$ ) in favor of 0.25% miconazole nitrate ointment. Decreases in the average diaper dermatitis severity index scores were observed in both treatment groups, and scores continued to decrease throughout the course of the study.

At the day 28 follow-up telephone interview, for the MITT subjects in the 0.25% miconazole nitrate ointment treatment group, 82% of subjects indicated that there was no recurrence of diaper rash; for subjects that did report a recurrence, 71% reported a mild rash. For MITT subjects in the vehicle control treatment group, 86% reported no recurrence of diaper rash; for subjects that did report a recurrence, 50% reported a mild rash. For rash outbreaks other than diaper rash, 91% of the subjects in the 0.25% miconazole nitrate ointment treatment group and 96% in the vehicle control group reported no recurrence.

At the day 28 follow-up telephone interview of subjects in the MITT population who had

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a therapeutic response of overall cure at the day 14 test-of-cure visit, 96% (25/26) in the 0.25% miconazole nitrate ointment treatment group reported no diaper rash, and 92% (24/25) reported no other type of rash at the day 28 follow-up telephone contact. For subjects in the vehicle control treatment group who had a therapeutic response of overall cure at the day 14 test-of-cure visit, 92% (11/12) reported no diaper rash, and 100% (12/12) reported not other type of rash.

The lack of recurrence or no further rash at 28 days can not be attributed to the presence of the miconazole nitrate in the treatment group. It may be due to better hygiene practices (e.g. more frequent diaper changes, better cleansing of the affected area). This is supported by the fact that the placebo treatment group had similar or better results than the miconazole nitrate treatment group.

#### Other findings

The applicant notes that a number of MITT subjects in the vehicle control treatment group withdrew from the study due to clinical failure/worsening/lack of improvement [59/124 (47%)], compared to the 0.25% miconazole nitrate ointment group [41/112 (4%)]. The applicant suggests that the active treatment was effective in maintaining subject participation from the onset of the study.

#### Conclusion for Clinical Study BT100USA/001

The miconazole nitrate MIC<sub>90</sub> ( $\leq 0.03$   $\mu\text{g/mL}$ ) for the isolates of *C. albicans* obtained during clinical trial BT100USA/001 is consistent with miconazole nitrate MIC data for *C. albicans* found in the literature. A miconazole nitrate MIC<sub>90</sub> of  $\leq 0.03$   $\mu\text{g/mL}$  suggests that the *C. albicans* should be easily eradicated by a preparation containing 0.25% miconazole nitrate. However, this is not reflected in the clinical response data, and overall therapeutic response (overall cure) where the clinical success rates was 40% and the therapeutic response rate was 26%. Also the 56% microbiological cure rate is counter intuitive to the fact that the *C. albicans* from the patients were so susceptible to miconazole nitrate. It would appear that elimination of *C. albicans* may not be the driving factor in resolving diaper dermatitis. The preparation containing the 0.25% miconazole nitrate did, however, do better than the vehicle control which suggests that the miconazole nitrate is playing some role in the treatment of diaper dermatitis at least in reference to the vehicle control for the miconazole nitrate. Whether the inclusion of miconazole nitrate in a preparation for the treatment of diaper dermatitis assists in the resolution of diaper dermatitis was not clearly proven in any of the clinical studies done by the applicant. However, because the preparation with 0.25% miconazole nitrate performed better than the placebo the inclusion of 0.25% miconazole nitrate may be beneficial. Data from this clinical trail provided no evidence that treatment failure in the 0.25% miconazole treatment group was the result of *C. albicans* developing resistance to miconazole nitrate.

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The Applicant concludes that all efficacy measures resulted in highly statistically significant outcomes in favor of the miconazole nitrate (0.25%) ointment. Based on the data in Table 6 the applicant states that the therapeutic response (i.e. clinically cured and microbiologically eradicated) demonstrated the superiority of 0.25% miconazole nitrate ointment over the vehicle control in the treatment of cutaneous candidiasis complicating diaper dermatitis.

### **OTHER CLINICAL TRIALS SUMMARIES PROVIDED BY THE APPLICANT**

#### **Clinical Study 10833/10842.33**

##### **An evaluation of the efficacy of BPC formula No. 610-58 in treatment of acute diaper dermatitis**

The following summary of this study is taken almost verbatim from the applicant's submission because there was no raw study data provided. Comments by this Reviewer will be noted by "this Reviewer".

This study was a placebo-controlled, randomized, double-blinded, parallel-group clinical trial conducted in the United States from November 1983 to June 1984, using 107 subjects with diaper dermatitis to evaluate the comparative efficacy of 0.25% miconazole nitrate ointment versus the vehicle control in treating acute infantile diaper dermatitis. The secondary endpoint of the study was to determine the prevalence of *C. albicans* associated with diaper rash and the influence of *C. albicans* on diaper rash severity.

#### Methodology

Subjects were required to have dermatological manifestations consistent with a diagnosis of diaper dermatitis rated according to a scale from 0 (none) to 4 (extreme erythema with erosions or ulcerations). Subjects were randomized to treatment with either 0.25% miconazole nitrate ointment (BPC Formula 610-58) or the vehicle control (BPC formula 610-61). The test medication was applied to the clinically affected area at each diaper change and after bathing of the infant.

The duration of the study was 7 days. Clinical evaluations were performed on days 0, 1, 3, 5, and 7. The investigator indicated the number of rash sites and assigned a score to each site on a scale from 0 (none) to 4 (extreme erythema with erosions and ulceration). Cultures for the presence of *C. albicans* were performed on Days 0 and 7; however, the presence of *C. albicans* was not an inclusion criterion.

#### Results

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A total of 107 subjects were enrolled in the study; 53 subjects were treated with the active ointment and 54 treated with the vehicle control. The study was completed by 99 subjects (51 in the 0.25% miconazole nitrate treatment group and 48 in the placebo ointment treatment group).

#### Efficacy results

The mean total rash score (sum of scores at all rash sites) was significantly lower for the active treatment group than for the vehicle control group from day 3 through day 7 ( $p < 0.050$ ). The mean total rash score on day 7 was 1.24 (day 0 = 5.04) for evaluable subjects in the active treatment group compared to 2.26 (day 5 = 5.10) for evaluable subjects in the placebo treatment group ( $p = 0.024$ ). On day 5, evaluable subjects in the active treatment group had an average number of 1.05 rash sites (day 0 = 2.44) compared to 1.47 rash sites (day 0 = 2.50) for the subjects in the vehicle control group ( $p = 0.44$ ). The difference between the two treatment groups in the number of rash sites on day 7 approached statistical significance ( $p = 0.054$ ).

Evaluable subjects who had moderate to severe diaper dermatitis at baseline and received active treatment had lower total rash scores on day 5 ( $p = 0.30$ ) and day 7 ( $p = 0.032$ ), with fewer rash sites on day 5 ( $p = 0.025$ ) and day 7 ( $p = 0.058$ ) than subjects in the vehicle control group. Among subjects with mild diaper dermatitis at baseline, the effects of the treatment did not differ ( $p > 0.700$ ).

On days 1, 3, 5, and 7, the investigators provided an overall rating of each subject's clinical response since baseline (i.e., clinically cured, improved, no change, worse, or recurred). Although not statistically different, 82% (40/49) of evaluable subjects in the active treatment group were clinically cured or improved on day 7, compared to 70% (23/46) of subjects in the vehicle control group.

At baseline, before treatment began, 43% (46/106) of subjects with cultures had *C. albicans* isolated from the anal site, while 34% (36/105) of subjects with cultures had *C. albicans* isolated at the inflamed rash site. When compared to subjects who did not have *C. albicans*, subjects with *C. albicans* had significantly higher total rash scores ( $p = 0.022$ ) when *C. albicans* was present at the anal site;  $p = 0.010$  then when *C. albicans* was present at the inflamed rash site).

Fifteen subjects showed the presence of *Candida* species other than *C. albicans*, primarily from cultures of the anal site. The presence of *Candida* species other than *C. albicans* was not associated with increased severity of rash, and those subjects responded equally well to active treatment or the vehicle control (Vol. 2.2, pg. 553). There was no evidence for emergence of other *Candida* species after the inflamed rash sites received treatment with 0.25% miconazole nitrate ointment.

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Among the 34 evaluable subjects with *C. albicans* isolated from inflamed rash sites at baseline, lower total rash scores were observed in the active treatment group compared to the vehicle control group on day 3 ( $p=0.043$ ), day 5 ( $p=0.038$ ), and day 7 ( $p=0.060$ ). Treatment failures and early terminations in the vehicle control group reduced the sample size for subjects positive for *C. albicans*. When the last observation was carried forward, the active treatment was significantly more effective than the vehicle control in treating rashes that were positive for *C. albicans* (day 3, day 5, and day 7; all at  $p<0.025$ ).

### **Conclusion**

From the summary of the data provided by the applicant in this submission it appears that the active treatment was more effective than the vehicle control in treating diaper dermatitis.

### **Reviewer's Comment**

It is interesting to note that species other than *C. albicans* did not seem to be involved in diaper dermatitis (Vol. 2.2, pg 553). Based on this information it may be appropriate to remove the *Candida* species results from the data used to calculate "Clinical Response" and "Therapeutic Response: Overall Cure" for the recent clinical study (BT100USA/001) since *Candida* spp. does not seem to elicit the diaper dermatitis rash.

### **Clinical Study 12966.37A**

The following summary of this study is taken almost verbatim from the applicant's submission because there was no raw study data provided. Comments by this Reviewer will be noted by "this Reviewer".

This study was a placebo-controlled, randomized, double-blind, parallel-group clinical trial conducted in Australia from February 1989 to March 1990, using 202 infants with diaper dermatitis. The objectives of the study were to evaluate the comparative efficacy of 0.25% miconazole nitrate ointment versus the vehicle control in the treatment of acute diaper dermatitis in infants, and to assess the relative efficacy of the treatments in the presence or absence of *C. albicans*.

### **Methodology**

Subjects were required to have dermatological manifestations consistent with a diagnosis of diaper dermatitis rated according to a scale from 0 (none) to 4 (extreme erythema with erosions or ulcerations). The presence of *C. albicans* at baseline was not an inclusion criterion. Subjects were randomized according to the global severity of the diaper dermatitis and assigned to treatment with either 0.25% miconazole nitrate ointment (BPC Formula 610-73), or the vehicle control (BPC Formula 610-115).

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The test medication was applied to the clinically affected area at each diaper change and after bathing. The duration of the study was seven days. Clinical evaluations were performed on days 0, 1, 3, 5, and 7. The investigator evaluated each infant and assigned a score to 11 rash sites using a scale of 0 (none) to 4 (extreme erythema with erosions or ulceration). Microbiological evaluations (i.e., culture for the presence of *C. albicans*) were performed on days 0 and 7 (or day of withdrawal).

#### Results

A total of 202 infants were enrolled in the study; 101 of these subjects were treated with the active ointment (of which 38 were culture positive) and 101 were treated with the vehicle control (of which 42 were culture positive). A total of 188 (96 in the 0.25% miconazole nitrate ointment group and 92 in the vehicle control treatment group) completed the study.

#### Efficacy results

On day 0, the mean number of rash sites for subjects in the 0.25% miconazole nitrate ointment treatment group was 4.53 and 4.49 for subjects in the vehicle control treatment group. On day 5, evaluable subjects in the active treatment group had a mean number of 1.91 sites compared to 3.03 rash sites for subjects in the vehicle control group ( $p<0.001$ ). On day 7 the mean number of rash sites for evaluable subjects in the active treatment group was 1.31 compared to 2.63 for the vehicle control group ( $p<0.001$ ). On 0, the mean total rash score for subjects in the 0.25% miconazole nitrate treatment group was 7.77 and 8.42 for subjects in the vehicle control group. The mean total rash score on day 5 was 2.29 for evaluable subjects in the active treatment group compared to 4.53 for subjects in the vehicle control group ( $p<0.001$ ). On day 7, the mean total rash score for evaluable subjects in the active treatment group was 1.61 compared to 4.03 for the vehicle control group ( $p<0.001$ ).

Beginning on day 3, evaluable subjects in the active treatment group had significantly higher percentage improvement in their total rash scores than subjects in the vehicle control group ( $p<0.005$ ). On day 7, subjects in the active treatment group had a 79% improvement in their total rash scores, compared to 45% in the vehicle control group ( $p<0.001$ ).

In the evaluation of global impression (i.e., rash described as none, mild, moderate, or severe) for the evaluable subjects, 91% and 94% of subjects in the active treatment group had mild or no diaper dermatitis present on days 5 and 7, respectively compared to 64% and 72% of the subjects in the vehicle control group (both  $p<0.001$ ).

The investigator assigned an overall rating of the subject's response (i.e., clinically cured,

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improved, no change, worse, or recurred). On day 7, 77% of the evaluable subjects in the active treatment group were clinically cured or improved compared to 53% of the subjects in the vehicle control group ( $p < 0.001$ ). In addition, significantly more evaluable subjects in the active treatment group were clinically cured or improved on day 3 ( $p = 0.014$ ) and day 5 ( $p < 0.001$ ) than in the vehicle control group.

The active treatment was particularly effective among subjects with moderate to severe diaper dermatitis at baseline. On day 7, 75% improvement from baseline in total rash scores was noted in the active treatment group compared to a 22% improvement among subjects in the vehicle control group ( $p < 0.001$ ).

At baseline, before treatment began, 31% of subjects had *C. albicans* isolated at the inflamed rash site, while 30% of subjects had *C. albicans* isolated from the anal site. When *C. albicans* was recovered at the inflamed rash site, subjects had more sites with (4.8 versus 4.4;  $p = 0.031$ ) higher total rash scores (8.1 versus 5.9;  $p < 0.001$ ) and a higher incidence of rashes judged to be of moderate to severe intensity (76% versus 35%;  $p < 0.001$ ).

Among evaluable subjects who had *C. albicans* isolated at their rash sites at baseline, 96% of subjects in the active treatment group no longer exhibited *C. albicans* at the rash site on day 7, compared to 4% of the subjects in the vehicle control group ( $p < 0.001$ ). Among evaluable subjects who had *C. albicans* isolated at their anal site at baseline, 92% of the subjects in the active treatment group no longer exhibited *C. albicans* at their anal site on day 7, compared to 15% of subjects in the vehicle control group ( $p < 0.001$ ). Among evaluable subjects which did not exhibit *C. albicans* at baseline, significantly more subjects in the active treatment group remained free of *C. albicans* at their rash sites (97% versus 84%) and at their anal site (99% versus 84%) than subjects in the vehicle control group (both  $p < 0.02$ ). There is not evidence for emergence of other *Candida* species after subjects were treated with the 0.25% miconazole nitrate ointment.

The active treatment was particularly effective among subjects with rashes that were positive for *C. albicans* at baseline. On day 7, an 83% improvement from baseline in total rash scores was noted in the active treatment group. When treated with vehicle control, *C. albicans* rashes were essentially unchanged when treatment ended (2% worse than baseline;  $p < 0.001$ ).

#### Conclusion

From the summary of the data the applicant has provided it appears that on day 7 there was a statistically significant difference ( $p < 0.001$ ) in the clinical cure rate between the subjects that had 0.25% miconazole nitrate ointment applied to the diaper dermatitis area versus those subjects that had the placebo applied to the diaper dermatitis area. Among the evaluable subjects who had *C. albicans* isolated at their rash sites at baseline and

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those that had placebo applied there was a statistically significant ( $p < 0.001$ ) difference in the placebo treated group that still had *C. albicans* at the site of the rash and those treated with the miconazole nitrate who did not have *C. albicans* at the site of the rash. This result suggests that the 0.25% miconazole is capable of eliminating *C. albicans* at the site of the diaper rash more effectively than is the placebo treatment.

### **Clinical Study 12966.37B**

The following summary of this study is taken almost verbatim from the applicant's submission because there was no raw study data provided. Comments by this Reviewer will be noted by "this Reviewer".

This study was a placebo-controlled, randomized, double-blind, parallel-group clinical trial conducted in Australia from December 1988 to November 1989, using 196 subjects with diaper dermatitis to evaluate the comparative efficacy of 0.25% miconazole nitrate ointment versus the vehicle control in the treatment of acute diaper dermatitis in infants.

#### **Methodology**

Subjects were required to have dermatological manifestations consistent with a diagnosis of diaper dermatitis rated according to a scale from 0 (none) to 4 (extreme erythema with erosions and ulcerations). Subjects were randomized according to the global clinical severity of their diaper dermatitis and assigned to treatment with either 0.25% miconazole nitrate ointment (BPC Formula 610-73), or the vehicle control (BPC Formula 610-115). The test medication was applied to the clinically affected area at each diaper change and after bathing the infant. The duration of the study was 7 days. Clinical evaluations were performed on days 0, 3, 5, and 7. The investigator evaluated each subject and assigned a score to 11 rash sites using a scale of 0 (none) to 4 (extreme erythema with erosions or ulceration).

#### **Results**

A total of 196 subjects were enrolled in the study. A total of 182 subjects (95 in the 0.25% miconazole nitrate ointment group and 87 in the vehicle control treatment group) completed the study.

##### **Efficacy Results**

On day 0, the mean number of rash sites for subjects in the 0.25% miconazole treatment group was 4.76 and 4.65 for subjects in the placebo treatment group. On day 5, evaluable subjects in the active treatment group had a mean number of 1.66 rash sites compared to 2.82 for subjects in the vehicle control group ( $p < 0.001$ ). On day 7, the mean number of rash sites for evaluable subjects in the active treatment group, was 1.01 compared to 2.55 for subjects in the vehicle control group ( $p < 0.001$ ).

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On day 0, the mean total rash score for subjects in the 0.25% miconazole nitrate ointment treatment group was 7.36 and 6.86 for subjects in the vehicle control treatment group. The mean total rash score on day 5 was 1.88 for evaluable subjects in the active treatment group compared to 3.77 on day 5 for subjects in the placebo treatment group. On day 7, the mean total rash score was 1.12 for evaluable subjects in the active treatment group compared to 3.65 for subjects in the vehicle control group.

On day 7, the mean percent improvement from baseline in total rash score was 85% for evaluable subjects in the active treatment group, compared to 49% for subjects in the vehicle control group ( $p<0.001$ ). The active treatment group also had significantly higher percent improvement from baseline on day 3 ( $p=0.002$ ) and day 5 ( $p<0.001$ ).

In the evaluation of global clinical impression on day 7 (i.e. rash described as none, mild, moderate, or severe), 95% of the evaluable subjects in the active treatment group had mild or no diaper dermatitis present, compared to 69% of the evaluable subjects in the vehicle control group ( $p<0.001$ ). Significantly more evaluable subjects in the active treatment group had mild or no diaper dermatitis present on day 3 ( $p=0.030$ ) and day 5 ( $p<0.001$ ) compared to the evaluable subjects in the vehicle control group.

An overall rating of clinical response since the previous evaluation was obtained on days 1, 3, 5, and 7. The investigator assigned an overall rating of the subject's response (i.e., clinically cured, improved, no change, worse, or recurred) since the previous evaluation. On day 7, 82% of the evaluable subjects in the active treatment group were clinically cured or improved, compared to 54% of the subjects in the vehicle control group ( $p<0.001$ ). In addition, significantly more evaluable subjects in the active treatment group were clinically cured or improved on days 3 and 5, compared to evaluable subjects in the vehicle control group ( $p=0.001$ ).

The active treatment was particularly effective among subjects with moderate to severe diaper dermatitis at baseline. On day 7, an 83% improvement from baseline in total rash was noted in the active treatment group, compared to a 32% improvement among subjects in the vehicle control group ( $p<0.001$ ).

### **Conclusion**

### **Reviewer's Comment**

The clinical summary result for study 12966.37B does not contain any information on the presence or absence of *C. albicans* after treatment. The summary data indicates that the active treatment group had better resolution of the diaper dermatitis than the vehicle treatment group. Without the mycology information this study does not provide any information to say that it was the elimination of *C. albicans* or *Candida* species that was

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the reason for clearing of the diaper dermatitis rash.

**OVERALL CONCLUSION**

The results of study BT100USA and data from other studies provided by the Applicant in this submission suggest that 0.25% miconazole nitrate may play some role in the treatment of diaper dermatitis but that role is not well defined. Data from clinical trail BT100USA provided no evidence that treatment failure in the 0.25% miconazole treatment group was the result of *C. albicans* developing resistance to miconazole nitrate.

**LABELING**

**APPLICANT'S PROPOSED LABEL**

The Applicant is proposing the microbiology statement in the following under pharmacology (Vol. 21, pg. 4).

**CLINICAL PHARMACOLOGY**

**b(4)**

**AGENCY'S PROPOSED LABELING**

Microbiology: The miconazole nitrate component on this product has been shown to have in vitro activity against *Candida albicans*, an organism that is associated with diaper dermatitis. The activity of miconazole nitrate against *C. albicans* is based on the inhibition of the ergosterol biosynthesis in the cell membrane. The accumulation of ergosterol precursors and toxic peroxides results in cytolysis. *Candida albicans* resistance to miconazole nitrate is unusual. The clinical significance of the in vitro activity of miconazole nitrate against *C. albicans* in the setting of diaper dermatitis is unclear.

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HFD-520

Lillian Gavrilovich, M.D.  
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Finalized 5/9/05

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Lillian Gavrilovich  
5/11/05 01:12:18 PM  
MEDICAL OFFICER

NDA#: 21-026 (Amendment to an Unapproved Application)

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Johnson & Johnson Consumer Companies

**Division of Anti-Infective Drug Products  
Clinical Microbiology Review # 1  
Dermatology Consult HFD-540**

**NDA#: 21-026 (Amendment to an Unapproved Application)**

**Date Completed: 5/2/00**

**Applicant:**

Johnson & Johnson Consumer Companies, Inc.

199 Grandview Road

Skillman, NJ 08558-9418

**Contact Person:**

Diana L B Uhl, Manager

Drug Regulatory Affairs

908-874-1700

**Therapeutic Type:** Antifungal

**Providing for:**

Treatment of moderate to severe diaper dermatitis where *Candida albicans* may be a contributing factor.

**Product Name:**

Proprietary: Pediastat™

Established Name: Miconazole nitrate diaper rash ointment, 0.25%

Code Name/Number: Zoom

Chemical Name: Miconazole nitrate (2,4-dichloro-β(2,4-dichlorobenzyl oxy)phenethyl) imidazole nitrate

Chemical formula (Empirical): C<sub>18</sub>H<sub>14</sub>Cl<sub>4</sub>N<sub>2</sub>O•HNO<sub>3</sub>

Molecular weight: 479.16

**Dosage form:** Topical ointment

**Strength:** 0.25% (2,500 µg/g) Miconazole nitrate

**Route of Administration:** Topical

**Dosage/Duration:** 7 days maximum

**Dispensed:** Over the counter (OTC)

**Initial Submission Dates**

Received by CDER: 1/24/00

Received by Reviewer: 2/16/00

Review Completed:

**Supplements/ Amendments:** Not applicable

**Related Documents:**

NDA 21-026 dated 8/28/98

**Remarks:**

This is a review of the resubmission information provided by Johnson & Johnson in response to a not approvable letter dated 6/28/1999. The not approvable letter was issued because of clinical and chemistry deficiencies. The clinical concerns the agency expressed were that yeast, in particular *Candida albicans*, may develop resistance to miconazole when it is used in the manner proposed and how clinical studies need to be conducted in order to determine the efficacy of the miconazole preparation (volume 1, pg. 28).

**FDA's Comment in Letter Dated 6/28/1999**

**CLINICAL**

1. The indication requires clear-cut definition so that the product may be recommend for the target population who can receive the clinical benefit without introducing the risk of drug resistance through indiscriminate use. An indication for the treatment of moderate or severe diaper dermatitis in association with *C. albicans* infection in infants may be acceptable, if a clinical trial, in which the severity of disease is properly defined and *C. albicans* infection is demonstrated both by wet mount examination of pseudohyphae and by culture, shows superiority of miconazole nitrate 0.25% ointment over the ointment base.

This Reviewer's summary of the applicant's responses to the issues raised in the FDA comment above follows (vol. 1, pg. 28-29). The applicant has provided more detail in the submission than indicated in this summary. This review will critique the applicant's complete responses.

**Reviewer's Summary**

The role of *C. albicans* in diaper dermatitis.

- *C. albicans* can be demonstrated in many, but not all, patients with diaper dermatitis.
- *C. albicans* can be a part of the fecal flora and then can be introduced into the diaper area with bowel movements. Hydrated, occluded conditions created by the diaper predispose for infection by *Candida*.
- *C. albicans* need not be invasive or even viable to contribute to diaper dermatitis: either cellular fragments or supernatant from disrupted *Candida* can, under occlusion,

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produce irritant dermatitis in normal volunteers.

Selection of Treatment for Diaper Dermatitis.

• In clinical practice the diagnosis of diaper dermatitis is commonly made on clinical criteria alone. Empiric therapy with anti-infectives usually encompasses the major etiological agents that may cause diaper dermatitis such as *C. albicans*, *Staphylococcus aureus*, and Gram-negative organisms.

Laboratory tests provide information in the diagnosis of diaper dermatitis relevant to the potential cause(s). This information can provide the basis for the appropriate supportive treatment as well as the appropriate use of anti-infective agents.

*C. albicans* Resistance to Miconazole

• Miconazole is widely used in prescription and non-prescription products, including extensive use for vaginal yeast infections; in addition to medical use; azole molecules are widely used in agriculture. Despite this extensive use, experience indicates that true resistance has occurred only in individuals with compromised immune function.

• *C. albicans* resistance to miconazole has not emerged as a clinical problem.

• We conclude from these considerations that PEDIASSTAT™ would have a negligible effect on the selection of resistant *C. albicans*.

**Applicant's Proposed Indication**

In view of the above, we (the applicant) propose the following indications for PEDIASSTAT™:

**INDICATED FOR INFANTS WITH DIAPER DERMATITIS**

**REVIEWER'S CONCLUSION**

The microbiology portion of this application is unacceptable until the Microbiology issues indicated in this review are adequately addressed.

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## **INTRODUCTION**

The resubmission package contains no new microbiology data generated by studies sponsored by Johnson & Johnson. The FDA expressed their concern in the not approvable letter dated 6/28/99 to the applicant about the possibility of yeast, particularly *Candida albicans*, developing resistant to miconazole when the applicant's miconazole preparation is used in the manner being proposed. The applicant has responded in this communication to this concern. The applicant has also provided their impression on how diaper dermatitis is diagnosed in the physician offices. They have provided this information to support their opinion on how a clinical trial might be conducted to determine the efficacy of the miconazole preparation.

## **EPIDEMIOLOGY STUDIES (Published Literature)**

A literature search for "*Candida albicans*" and "diaper rash" was conducted (3/00) using PubMed software at National Library of Medicine. A search of the literature produced some papers published within the last several years dealing with the current thoughts on the prevention, and diagnosis of diaper dermatitis. A few recent papers were found on the development of resistance to miconazole among yeast organisms. No papers were found in relation to the development of resistance to miconazole when it is used for the treatment of diaper dermatitis.

## **OVERVIEW OF THE ETIOLOGY OF DIAPER DERMATITIS**

Microbial factors have long been viewed as important etiological factors in diaper dermatitis (1-4). A variety of organisms, including *Staphylococcus aureus*, and Gram-negative organisms (e.g. *Escherichia coli* and *Proteus* spp.) have been recovered from inflamed rash areas (5). *Candida albicans* is implicated in the maintenance or worsening of the condition (5-7). In conditions of warmth and moisture, as under an occlusive diaper, *Candida albicans* can proliferate on the skin surface and then penetrate the stratum corneum to induce inflammation (7-11). Furthermore, low numbers of *Candida albicans* are capable of inducing dermatitis (5, 12). The dermatitis produced by *Candida albicans* is typically erythematous papules or vesicles involving the inguinal folds as well as the genitals, buttocks, and inner thighs. While *Candida albicans* is not routinely found on normal skin, it is present in the gastrointestinal tract, and it is presumably introduced via the feces (9). Reports on the presence of *Candida* vary. Recovery of the organism in up to 77% of subjects with diaper dermatitis has been reported (13).

## **DIAGNOSIS OF THE ETIOLOGIC AGENT OF DERMATITIS**

The literature is ambiguous as to what the most common approach among physicians is to diagnosing the etiologic agent that may be causing diaper dermatitis when an infant is first seen with the condition. Some literature supports the use of a KOH (potassium hydroxide) wet mount looking for the presence of yeast organisms or culture of the infected site for the presence of yeast organisms because the differential diagnosis includes other eruptions that may coexist with candida infection (14, 15). Other literature supports recognition of the entity by characteristics of its dermatological manifestations

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(16, 17).

**IN VITRO STUDIES****ANTIMICROBIAL SPECTRUM OF ACTIVITY**

It should be noted that the interpretation of the in vitro susceptibility data below is difficult because much of the data is based on non-standardized susceptibility testing methods.

Between 1980 to 1986 a total of 2602 isolates belonging to 107 fungal species, 5 species of Actinomycetales and one alga were tested for sensitivity to miconazole nitrate by Janssen Pharmaceutica NV (18). Of the 2602 isolates tested, 1740 (Table 1) were isolates of the five species most commonly associated with vaginal candidiasis. 1328 isolates of *Candida albicans*, 76 isolates of *Candida tropicalis*, 74 isolates of *Candida parapsilosis*, 45 strains of *Candida krusei* and 217 strains of *Candida (Torulopsis) glabrata* were evaluated to determine the concentration of miconazole nitrate necessary to completely inhibit development of the organisms. Results with these organisms are listed in Table 1.

Table 1

**Antimicrobial Activity of Miconazole Nitrate**

Species	# strains Tested	Number of strains inhibited at miconazole nitrate concentration ( $\mu\text{g/mL}$ )					
		0.01	0.1	1.0	10	100	>100
<i>C. albicans</i>	1328	52	155	678	441	1	1
<i>C. tropicalis</i>	76	0	12	37	27	0	0
<i>C. parapsilosis</i>	74	0	21	39	14	0	0
<i>C. krusei</i>	45	1	5	19	20	0	0
<i>C. glabrata</i>	217	2	8	163	43	1	0

Growth of most isolates was inhibited at miconazole nitrate concentrations of 10  $\mu\text{g/mL}$  or lower. In the case of *Candida albicans*, 67% of the isolates were inhibited at miconazole nitrate concentrations of 0.01 to 1.0  $\mu\text{g/mL}$ . Only 2 of 1740 isolates (0.12%) required a miconazole nitrate concentration of 100  $\mu\text{g/mL}$  to inhibit growth. Only one isolate of *Candida albicans* was not inhibited at a miconazole nitrate concentration of 100  $\mu\text{g/mL}$ . The frequency of more resistant MICs is low among these historical data from a large number of isolates.

A compilation of the MIC ranges for a variety of *Candida* species to miconazole is given below in Table 2 (19).

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Table 2

MIC Ranges for Miconazole Against a Variety of *Candida* species

<u>Organism (number of isolates)</u>	<u>MIC (<math>\mu\text{g/mL}</math>) range</u>
<i>Candida albicans</i> (1815)	0.016 – 100
<i>Candida glabrata</i> (224)	0.016 – 64
<i>Candida krusei</i> (40)	<0.063 – 6.25
<i>Candida parasilopsis</i> (54)	0.016 – 32
<i>Candida tropicalis</i> (172)	0.16 - 32

In 1982, Johnson & Johnson Baby Products Company did a study to determine the effect of zinc oxide in the formulation on miconazole nitrate (20). A test was run in vitro against *Staphylococcus aureus* and *Candida albicans*. The study showed that a combination of miconazole and zinc oxide in this test system exhibited a synergistic effect in the ability to inhibit growth of *S. aureus*. When tested with *Candida albicans*, low doses of the zinc oxide decreased the efficacy of miconazole nitrate, while higher doses showed a synergistic effect.

## MECHANISM OF ACTION:

The mode of action of imidazole derivatives has been investigated at the biochemical as well as the morphological level (21-27). The activity of miconazole is based on the inhibition of the ergosterol biosynthesis in the cell membrane of the microorganism. The major effects of imidazoles and triazoles on fungi are inhibition of sterol 14- $\alpha$ -demethylase, a microsomal cytochrome P-450-dependent enzyme system. Imidazoles and triazoles impair the biosynthesis of ergosterol for the cytoplasmic membrane and lead to the accumulation of 14- $\alpha$ -methylsterols. The accumulation of ergosterol precursors and toxic peroxides results in cytolysis (2, 28).

*Candida albicans* cells have been observed to exhibit progressive cytoplasmic deterioration and permanent shape changes resulting in complete cell necrosis depending on the dose and duration of exposure to miconazole nitrate (29-31). Early studies of miconazole nitrate showed that this agent affects the permeability of the cell membrane of sensitive cells (21-23). Cell membrane effects are evidenced by leakage of potassium ions and phosphorus containing compounds. Low fungistatic concentrations of miconazole nitrate inhibit the uptake of purines and glutamine by *C. albicans* (21). These changes in the cell membrane are consequences of interference with biosynthesis of lipids in the fungal cell, especially with the synthesis of sterols (12, 27). Sterols are components of many biological membranes, and an alteration in the amount and composition of sterols in newly formed membranes affects cellular structure

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and function. Ergosterol is the main sterol of fungal cell membranes. Van den Bossche and his associates (26, 27) have shown that low concentrations of miconazole nitrate inhibit the incorporation of [ $^{14}\text{C}$ ] acetate into ergosterol in *C. albicans*. This inhibition coincides with an accumulation of lanosterol-like sterols, i.e., sterols with a 14- $\alpha$ -methyl group in their structure. The accumulation of C14-methylsterols suggests that miconazole nitrate is a potent inhibitor of one of the metabolic steps involved in the demethylation at the C14 site. The faulty membranes produced from such action lead to inhibition, usually manifested as a modest but significant reduction in growth rate. At concentrations greater than  $10^{-5}$  mol ( $\sim 4\mu\text{g/mL}$ ), miconazole nitrate exerts direct physiochemical cell damage against *Candida albicans* evident as a rapid and pronounced lethal action (28, 29).

Miconazole nitrate has been shown to have an effect on oxidative and peroxidative enzymes (31, 32). Fungi possess a series of oxidative enzymes that are required for respiratory and metabolic functions including cytochrome C oxidase and Nicotinamide adenine dinucleotide [reduced form]- (NADH-) dependent oxidase. Oxidative pathways lead to the production of hydrogen peroxide, which, if not broken down, is toxic to the cell. The normal cell, therefore also possesses cytochrome C peroxidase and catalase, two enzymes that break down peroxide and thus maintain cell viability. Treatment with low doses of miconazole nitrate results in production of greater amounts of peroxide as the consequence of increased NADH-dependent oxidase activity. Simultaneously, the activity of peroxidase is suppressed and that of catalase is enhanced. With fungicidal doses of miconazole nitrate, NADH-dependent hydrogen peroxide production continues, whereas the activity of both peroxidase and catalase is totally inhibited. The intracellular buildup of hydrogen peroxide in toxic concentrations may contribute to the observed degeneration of subcellular structures that precedes cell death.

Typically, the published work pertaining to structural changes after imidazole treatment has involved yeast-phase cells of *C. albicans* (33-35). The effects of low levels of miconazole nitrate on morphology are similar and primarily involve alterations of the cell membrane, changes in cell volume and defective cell division. Deposition of abnormal membranous elements near the cell wall is characteristic of cells treated with a low dose ( $0.05\mu\text{g/mL}$ ) and is probably the morphologic translation of the effects on lipid biosyntheses.

Involution of internal organelles of fungal cells occurs after exposure to higher fungistatic concentrations of miconazole nitrate; the central vacuole becomes enlarged and the number of peroxisomes increases. The cells become angular in shape, most probably as an expression of the loss of osmotic resistance. Necrotic changes involving the great majority of cells are seen in the presence of fungicidal concentrations of miconazole nitrate ( $5\text{-}50\mu\text{g/mL}$ ) (35, 36).

The imidazole group of miconazole is subject to protonation (pKa approximately 6.5). Studies have suggested that the direct lethal effect of miconazole against *C. albicans* require nonprotonated drug molecules. Viability studies have suggested that the direct lethal effect of miconazole is inhibited with increasing as well as decreasing pH (i.e., pH

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&lt;6.0 and &gt;7.0) (37).

## MECHANISM (S) OF RESISTANCE

Resistance to the azole antimicrobials occurs because: 1) there is a modification in the quality or quantity of the enzyme associated with the production of ergosterol, 2) there is reduced access to the target enzyme, and 3) there is a combination of 1 and 2. As of yet there are no reports of modification of azole antimicrobials as a mechanism of resistance (22).

There have been no well-controlled studies addressing the issue of resistance developing to miconazole when it is used to treat diaper dermatitis. Neither have there been reports in the literature suggesting that such use has brought about diaper dermatitis cause by *C. albicans* that is refractory to treatment with miconazole. The development of *C. albicans* resistant to the azole class of antifungals have been reported when used in the treatment modality of patients with *Candida* vulvovaginitis, cancer patients and AIDS patients (38).

Development of resistance to miconazole nitrate is infrequent. It has been difficult to isolate resistant mutants of *Candida albicans* in the laboratory (39, 40). In one laboratory study, no mutant with significantly greater resistance to miconazole nitrate could be induced to appear following repeated passages on gradient plates (39). However, these laboratory experiments carry with them the uncertainties of conclusions associated with any negative mutant hunt.

The prime concern about resistance to miconazole nitrate has been most extensively viewed as a potential cause in the etiology of recurrent vulvovaginal candidiasis. To adequately address the role of antifungal resistance as a potential mechanism for this condition, a longitudinal susceptibility analysis of 177 *C. albicans* isolates collected from 50 *C. albicans* patients over a period of 3 months to 7 years was performed (41). Antifungals tested included miconazole, clotrimazole, ketoconazole, itraconazole and fluconazole. Results of in vitro sensitivities of multiple *C. albicans* isolates convincingly showed that numerous isolates collected for up to 7 years from women with recurrent vulvovaginal candidiasis were equally sensitive to all antifungals tested by the current NCCLS reference method (42) for susceptibility testing of yeasts. Successive isolates from individual patients did not show increased resistance to any drug despite long-term exposure to azoles. Additionally, there was no increase in minimal inhibitory concentrations (MICs) as a result of prolonged therapy, and the MICs from the majority of longitudinal isolates collected from individual women did not shift with any drug over time. These results suggest that episodes of recurrent vulvovaginal candidiasis caused by *C. albicans* are attributable to mycological failure to respond to therapy rather than development of in vitro resistance to azole antifungals. Although development of resistance was not observed in this study, the products labeled for vulvovaginal candidiasis have a much higher content of miconazole (2%) (43). These vulvovaginal studies may not be applicable to predicting emergence of resistance of *Candida* to miconazole for the product, which is the subject of this application due to its reduced content of miconazole.

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In a recent study, Boschman and associates (38) looked at 13-year evolution of azole resistance in yeast isolates from cancer patients at a large medical center. The azoles studied included fluconazole, ketoconazole, itraconazole and miconazole. From 1984 to 1992 all of the yeast isolates tested were susceptible to fluconazole, ketoconazole, and miconazole. Itraconazole was not introduced for use until 1996. During the years 1994, 1995, 1996, and 1997 83%, 84%, 97% and 97% of yeast isolates remained susceptible to miconazole. A similar percentage of strains for fluconazole, ketoconazole, and itraconazole remained susceptible to these antifungals.

Two studies (44, 45), closer to the applicant's request for the use of miconazole were found and reviewed. One study (44) compared the effectiveness of over-the-counter products containing 2% miconazole nitrate to inhibit the growth of *C. albicans*. The author's conclusions were that the over-the-counter products were as effective as mycostatin cream in inhibiting the growth of *C. albicans* and that the 2% miconazole nitrate was also inhibitory to *C. albicans* at greater dilutions than five other antifungal products containing chloroxylonol and clotrimazole. The other study (45) evaluated the use of a miconazole containing paste in the treatment of diaper dermatitis. The authors concluded that miconazole-nitrate-containing paste where the concentration of miconazole is a 2% reduces the erythema and corneum alterations of the skin and provides the diapered skin with an improved microbial environment. Neither reference 44 or 45 mentions miconazole resistant *C. albicans*.

In a paper published in 1987 (46) Beggs noted that miconazole at concentrations  $>10^{-5}$  mol can induce direct physiochemical damage to late lag and early to mid logarithmic phase yeast cells of *C. albicans*. As stationary phase is approached, however, susceptibility to this direct-lethal action (DLA) is lost and early to mid stationary phase cells are quite resistant to being killed (46). In a later paper by Beggs et al (47) it was demonstrated that miconazole at a sub-level-DLA of  $2.0 \times 10^{-6}$  mol ( $\sim 0.8 \mu\text{g/mL}$ ) reverted *C. albicans* cells in early logarithmic phase (DLA-susceptible) to DLA resistant. In a more recent study (48) Beggs suggests from experimental evidence that in the presence of a sub-level-DLA concentration of miconazole that important alterations in existing membrane material and not extensive incorporation of faulty components into newly synthesized membranes occurs. Beggs proposes that without the proper building components faulty membrane is produced, resulting in impaired growth. Coincidentally, these faulty membranes lack chemical components and structural configurations required for DLA of miconazole.

Recent research has shown that resistance to antifungals in *C. albicans* having to do with efflux is mediated by certain genes (22). To date there seem to be two general gene groups mediated resistance by efflux. These groups are referred to as the MFS (major facilitator superfamily and the ABC (ATP-binding cassette) superfamily of proteins (22). To date, eight genes for ABC transporters have been identified in *Candida*. An example of such a gene is CDR1 (*Candida* drug resistance gene), which is involved in resistance to azoles (22). Researchers have shown that transient expression of this gene occurs when there is exposure to miconazole (49).

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**HUMAN AND ANIMAL STUDIES**

## Pharmacokinetics/Bioavailability

The site of microbiological activity for this drug product is on the skin surface, epidermis and dermis, correlating to the site of the candidal infection. The pharmacokinetic profile of miconazole nitrate is not provided in this application.

## Animal Prophylactic and Therapeutic Studies

The effectiveness of miconazole nitrate has been demonstrated in several experimental animal models. Van Cutsem and Thienpont (50) demonstrated the efficacy of miconazole nitrate given orally or topically against cutaneous infections with *Candida albicans*, *Trichophyton mentagrophytes*, and *Microsporum canis* in guinea pigs. In another study, all mice given miconazole base intramuscularly and subcutaneously 4 days after infection with 50 or 100% lethal doses of *Coccidicoides immitis* were protected, whereas 60 to 100% of the untreated mice succumbed (51). Cultural assays of lung tissue confirmed that the drug limited proliferation of the fungus at that site. Miconazole nitrate, at concentrations of 1.0 and 2.0%, was shown to be effective in the topical treatment of experimentally induced *Candida* keratitis. The drug proved effective in reducing inflammation and producing mycological cures in these developmental animal model experiments (52).

**CLINICAL EFFICACY**

## Clinical Microbiology

Susceptibility testing is not routinely warranted. In those situations where the diaper dermatitis does not resolve appropriately when a miconazole-containing product has been used culture of the dermatitis and susceptibility testing of any yeast isolates may be appropriate to guide further care. Susceptibility testing should be done using a standardized methodology (42). There are no interpretive criteria established for miconazole nitrate that are recognized by the FDA and the National Committee for Clinical Laboratory Standards has not proposed interpretive criteria (42).

## OTHER

The applicant has included in their submission letters from Dr. Michael Rinaldi (vol. 1 pg. 34) and Dr. Frank Odds (vol. 1 pg. 37). Both of these letters speak to the issue of resistance developing to miconazole. The reviewer agrees with the premise of the comments of both Drs. Rinaldi and Odds. The development of miconazole resistance in *Candida* spp. except in certain patient populations (immunocompromised, HIV) when miconazole has been used in higher concentrations than the concentration being proposed by the applicant ( $\geq 1\%$  topically or 5 – 9  $\mu\text{g/mL}$  systemically) has not been a major concern. Both individuals, however, do not specifically address the use of the concentration of miconazole (0.25%) being proposed by the applicant in this context.

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### **Package Insert**

Isolates Approved

*Candida albicans*

Interpretive Criteria Established

In the event that susceptibility testing of any yeast isolates is deemed necessary the appropriate references should be consulted for susceptibility testing methods (42). There are no interpretive criteria established for miconazole nitrate that are recognized by the FDA and the National Committee for Clinical Laboratory Standards has not proposed interpretive criteria (42).

### **SUMMARY**

The applicant is proposing the use of a topical ointment for treating diaper dermatitis that is the result of infection with *Candida albicans*. The ointment has as its active antifungal agent miconazole in a concentration of 0.25% (2,500 µg/g).

There are no well-controlled studies that have looked at the efficacy of miconazole containing ointments for the treatment of diaper dermatitis due to *C. albicans*. Because of this fact it is important to conduct well-controlled studies to determine the efficacy of this preparation. These studies at a minimal need to compare the efficacy of the preparation with and without the presence of the miconazole.

### **The role of *C. albicans* in Diaper Dermatitis**

The literature supports the fact that *C. albicans* plays a role in causing diaper dermatitis. As noted by the applicant hydrated, occluded conditions at the site of the dermatitis predispose to infection with *C. albicans*. The literature, however, is unclear as to whether simply eliminating or reducing the numbers of *C. albicans* present will resolve the condition because well-controlled studies have not been conducted. The applicant is encouraged to conduct such studies to better define the role their preparation may play in treatment of diaper dermatitis.

### **Diagnosis of Diaper Dermatitis.**

The literature is ambiguous as to how diaper dermatitis is diagnosed (clinical and/or by KOH wet mount and or culture). Because this is a study to determine the efficacy of a preparation in treating diaper dermatitis due to *C. albicans* the applicant needs to definitely demonstrated the presence of yeast (i.e. *C. albicans*), as the causative agent of the dermatitis. This can only be done by culture of the area to be treated with the preparation prior to its use.

## **Treatment of Diaper Dermatitis**

Appropriate clinical trials need to be conducted because it has not been demonstrated that the applicant's product containing a 0.25% concentration of miconazole nitrate is efficacious in an alkaline environment in eliminating *C. albicans* when diaper dermatitis is present.

### ***C. albicans* Resistance to Miconazole**

The applicant has provided information to support their position that *C. albicans* becoming resistant to miconazole due to the use of their preparation will not be a significant problem. It is agreed that resistance to miconazole has not been a problem, except, in specific patient populations, such as AIDS patients. It needs to be recognized, however, that generally the concentration of miconazole used is greater than what is contained in the applicant's preparation (1 and 2% vs. 0.25%). Evidence that the concentration of miconazole proposed by the applicant (0.25%) would not provide an environment conducive to the selection of miconazole-resistant organisms has not been provided either in applicant's submission or in the literature. Because of: 1) the limited experience with lower than 2% concentrations of miconazole, 2) the development of resistant strains of *C. albicans*, and 3) the fact that recent literature suggests that low concentrations may induce resistance mechanisms, the applicant needs to design their clinical studies so that the development of miconazole-resistant *C. albicans* can be detected.

### **Other**

#### In vitro demonstration of the activity of miconazole under conditions of use.

The concentration of miconazole 0.25% (2,500 µg/g) in the preparation under review when tested in-vitro at a pH of 6.8 – 7.0 is sufficient to inhibit the growth of better than 90% of *Candida albicans* isolates. However, it has been demonstrated that the activity of miconazole may be decreased at either alkaline or acidic pH. Because there is the potential for this topical ointment to be used in an alkaline environment, the activity of the miconazole at the concentration of 0.25% needs to be determined in vitro under alkaline conditions against *C. albicans*.

#### Lack of recognized susceptibility testing interpretive criteria for miconazole

There are no recognized susceptibility testing interpretive criteria for miconazole nitrate. Therefore the applicant will need to validate any interpretive criteria that they use for interpreting microbiology and clinical outcome data.

### **Labeling**

While there is an association of *C. albicans* with some cases of diaper dermatitis the literature does suggest that there may be other organisms (bacteria, other species of

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yeast) which cause this entity.

Therefore the labeling should indicate that the product only be used in those situations where it is known that *C. albicans* is present.

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### **Education for proper use of product**

While there are appropriate times to use preparations containing miconazole to treat diaper dermatitis there are just as well inappropriate times. It is well established that over use of any antimicrobial can lead to the lack of its efficacy due to the development of resistant organisms. The applicant should be encouraged to provide educational information and information resources to the user of their preparation on the treatment of diaper dermatitis. This information should be designed so that inappropriate use of the miconazole preparation will be diminished and the user of the product will have enhanced knowledge as to when it might be appropriate to obtain medical assistance. Resources such as the American Academy of Pediatrics, Elk Grove Village, IL should be considered.

### **CONCLUSION**

The microbiology portion of this application is unacceptable until the Microbiology issues are addressed.

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*Frederic J. Marsik 5/2/00*

Frederic J. Marsik, Ph.D.  
Review Microbiologist

- cc: Original 21-026  
HFD-520 Divisional File  
HFD-540/MO/J Wilkin  
HFD-520/Micro/F Marsik  
HFD-540/MO/H Ko  
HFD-540/Chemist/J Timmer  
HFD-540/Pharm/A Nostrandt  
HFD-880/Biopharm/V Tandon  
HFD-540/CSO/M Wright

**Concurrence Only**

HFD-520/Dep/Dir/L. Gavrilovich *LB 5/11*

*TJ 5/13/00*

HFD-520/TLMicro/A. T. Sheldon Jr.

*BD Initialed 4/20/00 Final 5/1/00 AJP*

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REVIEW FOR HFD-540

OFFICE OF NEW DRUG CHEMISTRY  
MICROBIOLOGY STAFF HFD-805  
Microbiologist's Review # 1 of NDA 21-026

April 19, 2000

A. 1. APPLICATION NUMBER: NDA 21-026

APPLICANT: Johnson & Johnson  
199 Grandview Road  
Skillman, NJ 08558  
(tel) 908-874-1700  
(fax) 908-874-1118

2. PRODUCT NAME: Pediastat™

b(4) 3. DOSAGE FORM: Miconazole nitrate (0.25%) Diaper Rash Ointment supplied in 30g tubes and 5g sample tubes.

4. METHOD OF STERILIZATION: None (non-sterile product).

5. PHARMACOLOGICAL CATAGORY and/or PRINCIPLE INDICATION: Synthetic antifungal indicated for the treatment of moderate to severe diaper dermatitis where *Candida albicans* may be a contributing factor.

B. 1. DATE OF INITIAL SUBMISSION: 8/24/98

2. DATE OF RESUBMISSION: 1/24/00

3. DATE OF CONSULT: 3/8/00

4. ASSIGNED FOR REVIEW: 4/10/00

C. REMARKS: The 1/24/00 resubmission was filed in response to a NA letter issued 6/28/99. A microbiology consult request was not issued for the original submission. Therefore, a microbiology review of the original submission was not performed.

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**D. CONCLUSIONS:**

The application is approvable pending resolution of issues concerning microbial limits testing of the drug product. Specific comments are provided in sections "E. REVIEW NOTES" and "List of Microbiology Deficiencies and Comments".

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Neal Sweeney, Ph.D.

cc:

Original NDA 21-026  
HFD-540/Division File  
HFD-540/Millie Wright  
HFD-805/Consult File/N. Sweeney

Drafted by: Neal Sweeney, April 19, 1999  
R/D initialed by P. Cooney, April 19, 1999

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3 Page(s) Withheld

2 Trade Secret / Confidential

     Draft Labeling

     Deliberative Process

King

MAY 24 1999

Consultative Review to HFD-540  
Division of Anti-Infective Drug Products (HFD-520)  
Clinical Microbiology Review Notes #1

**NDA # 21-026**

**DATE COMPLETED: 9 APR 1999**

**SPONSOR(IND)/APPLICANT(NDA):**

Johnson and Johnson Consumer Companies  
199 Grandview Road  
Skillman, NJ 08558-9418

**CHEM/THER. TYPE:** Imidazole

**SUBMISSION REVIEWED:** Original NDA  
**PROVIDING FOR:** Microbiology data

**PRODUCT NAMES(S):**

Proprietary: Pediastat

Non-Proprietary/USAN: miconazole

**DOSAGE FORMS(S)** Ointment

**STRENGTHS:** 0.25%

**ROUTE(S) OF ADMINISTRATION:** Topical

**PHARMACOLOGICAL CATEGORY:** antiinfective

**DISPENSED:**  X  Rx   OTC

**INITIAL SUBMISSION:**

Received by CDER: 24 AUG 1998  
Received by Reviewer: 27 JAN 1999  
Review Completed: 9 APR 1999

**AMENDMENT(S)**

Received by CDER: N/A  
Received by Reviewer:  
Review Completed:

**REMARK(S):**

Portions of this NDA were submitted electronically as a review aid to the Microbiology reviewer. The numbering of citations from this submission has been preserved within this review document; thus, the numbering of citations and tables in this review is discontinuous, and the designated numerals of individual citations are identical to the same numerals in the reference list of the original document. This renumbering convention is a proactive way to allow easier navigation between the original submission and its derived review documents.

Electronic submission of the NDA text allows ready transferal of information from the submission to this review document. Significant portions of this document were electronically copied from the electronic submission and edited to reflect the FDA Reviewers' perspective.

This NDA was submitted in support of the treatment of diaper rash involving *Candida albicans*. *Candida albicans* has been listed in the Indications section of other dosage forms containing miconazole as the active ingredient. Miconazole appears to have ample in vitro activity against *Candida albicans*. However, other topical dosage forms have a miconazole content of 2% instead of the 0.25% in this ointment for diaper rash. This reduced amount of miconazole is still a large amount of miconazole in relation to the treatment dose of miconazole and the preponderance of low MICs for *Candida albicans* reported in this application.

**CONCLUSIONS and/or RECOMMENDATIONS:**

From the microbiological perspective, this application is approvable with the following text of the Microbiology subsection of the package insert:

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Revision Note: 4 MAY 1999

The package insert proposed by the applicant was significantly truncated to eliminate information that is not pertinent to the proposed indications. The proposed indications for the miconazole only include diaper rash involving *Candida albicans*.

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If this product is approved in its present form, the Microbiology subsection should remain as noted above in the Recommendations and Conclusions section.

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Microbiological Review Notes:

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## INTRODUCTION

Microbial factors have long been viewed as important etiological factors in diaper dermatitis. A variety of organisms, including *Staphylococcus aureus*, and Gram-negative organisms (e.g., *Escherichia coli* and *Proteus* spp.) have been recovered from inflamed rash areas.<sup>5</sup> *Candida albicans* is implicated in the maintenance or worsening of the condition.<sup>5-7</sup> In conditions of warmth and moisture, as under an occlusive diaper, *Candida albicans* can proliferate on the skin surface and then penetrate the stratum corneum to induce inflammation.<sup>7-11</sup> Furthermore, low numbers of *Candida albicans* are capable of inducing dermatitis.<sup>5,12</sup>

The dermatitis produced by *Candida albicans* is typically erythematous papules or vesicles involving the inguinal folds as well as the genitals, buttocks, and inner thighs. While *Candida albicans* is not routinely found on normal skin, it is present in the gastrointestinal tract, and it is presumably introduced via the feces.<sup>9</sup> Reports on the presence of *Candida* vary, with recovery of the organism in up to 77% of subjects with diaper dermatitis.<sup>13</sup>

## PRECLINICAL EFFICACY

### *In vitro*

#### Mechanism(s) of Action.

The mode of action of imidazole derivatives has been investigated at the biochemical as well as the morphological level.<sup>18-23</sup> The activity of miconazole is based on the inhibition of the ergosterol biosynthesis in the cell membrane of the pathogenic microorganism. At concentrations achieved during systemic use, the major effects of imidazoles and triazoles on fungi are inhibition of sterol 14- $\alpha$ -demethylase, a microsomal cytochrome P-450-dependent enzyme system.

Imidazoles and triazoles impair the biosynthesis of ergosterol for the cytoplasmic membrane and lead to the accumulation of 14- $\alpha$ -methylsterols. The accumulation of ergosterol precursors and toxic peroxides results in cytolysis.<sup>21,23</sup> *Candida albicans* cells have been observed to exhibit progressive cytoplasmic deterioration and permanent shape changes resulting in complete cell necrosis depending on the dose and duration of exposure to miconazole nitrate.<sup>24-26</sup>

Early studies of miconazole nitrate showed that this agent affects the permeability of the cell membrane of sensitive

cells.<sup>19-21</sup> Cell membrane effects are evidenced by leakage of potassium ions and phosphorus containing compounds. Low fungistatic concentrations of miconazole nitrate inhibit the uptake of purines and glutamine by *C. albicans*.<sup>19</sup> These changes in the cell membrane are consequences of interference with biosynthesis of lipids in the fungal cell, especially with the synthesis of sterols.<sup>22,23</sup>

Sterols are components of many biological membranes, and an alteration in the amount and composition of sterols in newly formed membranes affects cellular structure and function.<sup>22</sup> Ergosterol is the main sterol of fungal cell membranes. Van den Bossche and his associates<sup>22,23</sup> have shown that low concentrations of miconazole nitrate inhibit the incorporation of [<sup>14</sup>C]acetate into ergosterol in *C. albicans*. This inhibition coincides with an accumulation of lanosterol-like sterols, i.e., sterols with a 14- $\alpha$ -methyl group in their structure. The accumulation of C14-methylsterols suggests that miconazole nitrate is a potent inhibitor of one of the metabolic steps involved in the demethylation at the C14 site.

The faulty membranes produced from such action lead to inhibition, usually manifested as a modest but significant reduction in growth rate. At concentrations greater than  $10^{-5}$  Mole, miconazole nitrate exerts direct physiochemical cell damage against *Candida albicans* evident as a rapid and pronounced lethal action.<sup>24,26</sup>

Miconazole nitrate has been shown to have an effect on oxidative and peroxidative enzymes.<sup>29,30</sup> Fungi possess a series of oxidative enzymes that are required for respiratory and metabolic functions including cytochrome C oxidase and Nicotinamide adenine dinucleotide [reduced form]- (NADH-)-dependent oxidase. Oxidative pathways lead to the production of hydrogen peroxide, which, if not broken down, is toxic to the cell. The normal cell, therefore also possesses cytochrome C peroxidase and catalase, two enzymes that break down peroxide and thus maintain cell viability. Treatment with low doses of miconazole nitrate results in production of greater amounts of peroxide as the consequence of increased NADH-dependent oxidase activity. Simultaneously, the activity of peroxidase is suppressed and that of catalase is enhanced. With fungicidal doses of miconazole nitrate, NADH-dependent hydrogen peroxide production continues, whereas the activity of both peroxidase and catalase is totally inhibited. The intracellular buildup of hydrogen peroxide in toxic concentrations may contribute to the observed degeneration of subcellular structures that precedes cell death.

Typically, the published work pertaining to structural changes after imidazole treatment has involved yeast-phase cells of *C. albicans*.<sup>31-33</sup> The effects of low levels of miconazole nitrate on morphology are similar and primarily involve alterations of the cell membrane, changes in cell volume and defective cell division. Deposition of abnormal membranous elements near the cell wall is characteristic of cells treated with a low dose (0.05 µg/mL) and is probably the morphologic translation of the effects on lipid biosyntheses.

Involution of internal organelles of fungal cells occurs after exposure to higher fungistatic concentrations of miconazole nitrate; the central vacuole becomes enlarged and the number of peroxisomes increases. The cells become angular in shape, most probably as an expression of the loss of osmotic resistance. Necrotic changes involving the great majority of cells are seen in the presence of fungicidal concentrations of miconazole nitrate (5-50 µg/mL)<sup>33,34</sup>

#### **Antimicrobial Spectrum of Activity.**

Between 1980 to 1986 a total of 2602 isolates belonging to 107 fungal species, 5 species of Actinomycetales and one algae were tested for sensitivity to miconazole nitrate by Janssen Pharmaceutica NV.<sup>35</sup> Of the 2602 isolates tested, 1740 were isolates of the five species most commonly associated with vaginal candidiasis. 1328 isolates of *Candida albicans*, 76 isolates of *Candida tropicalis*, 74 isolates of *Candida parapsilosis*, 45 strains of *Candida krusei* and 217 strains of *Candida (Torulopsis) glabrata* were evaluated to determine the concentration of miconazole nitrate necessary to completely inhibit development of the organisms. Results with these organisms are listed in Table 2.

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Table 2

## Antimicrobial Activity of Miconazole Nitrate

Species	# strains Tested	Number of strains inhibited at miconazole nitrate concentration ( $\mu\text{g/mL}$ )					
		0.01	0.1	1.0	10	100	>100
<i>C. albicans</i>	1328	52	155	678	441	1	1
<i>C. tropicalis</i>	76	0	12	37	27	0	0
<i>C. parapsilosis</i>	74	0	21	39	14	0	0
<i>C. krusei</i>	45	1	5	19	20	0	0
<i>C. glabrata</i>	217	2	8	163	43	1	0

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Growth of most isolates was inhibited at miconazole nitrate concentrations of 10 µg/mL or lower. In the case of *Candida albicans*, 67% of the isolates were inhibited at miconazole nitrate concentrations of 0.01 to 1.0 µg/mL. Only 2 of 1740 isolates (0.12%) required a miconazole nitrate concentration of 100 µg/mL to inhibit growth. Only one isolate of *Candida albicans* was not inhibited at a miconazole nitrate concentration of 100 µg/mL. Although these studies were not performed using current NCCLS Reference methodology, the frequency of more resistant MICs is low among these historical data from a large number of isolates.

In 1982, a study was done by the Johnson & Johnson Baby Products Company to determine the effect of zinc oxide in the formulation on miconazole nitrate.<sup>36</sup> A test was run in vitro against *Staphylococcus aureus* and *Candida albicans*. The study showed that a combination of miconazole and zinc oxide in this test system exhibited a synergistic effect in the ability to inhibit growth of *S. aureus*. When tested with *Candida albicans*, low doses of the zinc oxide decreased the efficacy of miconazole nitrate, while higher doses showed a synergistic effect.

#### Mechanism(s) of Resistance Studies (Panel).

Development of resistance to miconazole nitrate is infrequent. It has been difficult to isolate resistant mutants of *Candida albicans* in the laboratory.<sup>37,38</sup> In one laboratory study, no mutant with significantly greater resistance to miconazole nitrate could be induced to appear following repeated passages on gradient plates.<sup>39</sup> However, these laboratory experiments carry with them the uncertainties of conclusions associated with any negative mutant hunt.

The prime concern about resistance to miconazole nitrate has been most extensively viewed as a potential cause in the etiology of recurrent vulvovaginal candidiasis. To adequately address the role of antifungal resistance as a potential mechanism for this condition, a longitudinal susceptibility analysis of 177 *C. albicans* isolates collected from 50 *C. albicans* patients over a period of 3 months to 7 years was performed.<sup>37</sup> Antifungals tested included miconazole, clotrimazole, ketoconazole, itraconazole and fluconazole. Results of in vitro sensitivities of multiple *C. albicans* isolates convincingly showed that numerous isolates collected for up to 7 years from women with recurrent

vulvovaginal candidiasis were equally sensitive to all antifungals tested by the current NCCLS Reference method for susceptibility testing of yeasts. Successive isolates from individual patients did not show increased resistance to any drug despite long-term exposure to azoles. Additionally, there was no increase in minimal inhibitory concentrations (MICs) as a result of prolonged therapy, and the MICs from the majority of longitudinal isolates collected from individual women did not shift with any drug over time. These results suggest that episodes of recurrent vulvovaginal candidiasis caused by *C. albicans* are attributable to mycological failure to respond to therapy rather than development of in vitro resistance to azole antifungals. Although development of resistance was not observed in this study, the products labeled for vulvovaginal candidiasis have a much higher content of miconazole. These vulvovaginal studies may not be applicable to predicting emergence of resistance of *Candida* to miconazole for the product, which is the subject of this application due to its reduced content of miconazole.

#### **Epidemiological Studies (Published Literature).**

A literature search for "*Candida albicans*" and "diaper rash" was conducted using PubMed software at NLM. No articles were found. When the search was broadened to "diaper rash" and screened for recent publications relating to treatment of diaper rash involving *Candida albicans*, no pertinent publications were found, especially ones dealing with miconazole.

#### ***In vivo***

#### **Pharmacokinetics/Bioavailability (Human and animal).**

The site of activity for this drug product is on the skin surface, epidermis and dermis, correlating to the site of the candidal infection. The pharmacokinetic profile of miconazole nitrate is provided in this application only to substantiate the safety of this product and is therefore not abstracted in this review.

#### **Animal Prophylactic and Therapeutic Studies.**

The effectiveness of miconazole nitrate has been demonstrated in several experimental animal models. Van Cutsem and Thienpont<sup>40</sup> demonstrated the efficacy of miconazole nitrate given orally or

topically against cutaneous infections with *Candida albicans*, *Trichophyton mentagrophytes* and *Microsporum canis* in guinea pigs. In another study, all mice given miconazole base intramuscularly and subcutaneously 4 days after infection with 50 or 100% lethal doses of *Coccidicoides immitis* were protected, whereas 60 to 100% of the untreated mice succumbed.<sup>41</sup> Cultural assays of lung tissue confirmed that the drug limited proliferation of the fungus at that site. Miconazole nitrate, at concentrations of 1.0 and 2.0%, was shown to be effective in the topical treatment of experimentally induced *Candida* keratitis. The drug proved effective in reducing inflammation and producing mycological cures in these developmental animal model experiments.<sup>42</sup>

### CLINICAL EFFICACY

#### Clinical Microbiology

No clinical laboratory susceptibility test is warranted for routine evaluation of this condition.

#### Package Insert.

#### Isolates Approved

*Candida albicans*

#### Interpretative Criteria Established.

No susceptibility testing breakpoints were proposed.

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HFD-540/Pharm/Nostrandt

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*9/3 5/24/99*

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**MICROBIOLOGY FILEABILITY**

On initial review of the NDA application:

	<u>YES</u>	<u>NO</u>
1. Is the microbiology section of the NDA organized in a manner to allow substantive review to begin?	X	
2. Is the microbiology section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X	
3. Is the microbiology section and other microbiologically pertinent sections of the NDA legible so that substantive review can begin?	X	

**HAS THE APPLICANT SUBMITTED:**

1. In vitro data in necessary quantity, using necessary clinical and non-clinical strains and using necessary numbers of approved laboratories to meet current Divisional standards for approvability of the product based on the submitted draft labeling?	X
2. Required animal model studies necessary for approvability of the product based on the submitted draft labeling?	X
3. Draft breakpoints and interpretive criteria in a manner consistent contemporary standards, in a manner which attempts to correlate criteria with clinical results of NDA studies, and in a manner to allow substantive review to begin?	X
4. All special studies/data requested by the Division during pre-submission discussions?	X
5. Draft labeling consistent with 201.56 and 201.57, current Divisional policy, and the design of the development package?	X
6. From a Microbiology perspective, is this NDA fileable? If NO, give reasons.	X

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