

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-026**

**MEDICAL REVIEW(S)**

**CLINICAL TEAM LEADER MEMO**  
**NDA 21-026**  
**VUSION Ointment**  
**(0.25% miconazole nitrate, 15% zinc oxide, and 81.35% white petrolatum)**

February 16, 2006

The current submission dated August 15, 2005 addresses the Non-Approval letter dated May 24, 2005 for this product in an adequate manner. Therefore, the Clinical Team recommends that this product be approved for the indication of adjunctive treatment of diaper dermatitis only when complicated by documented candidiasis (microscopic evidence of pseudohyphae and/or budding yeasts), in immunocompetent pediatric patients 4 weeks and older.

From the previous review cycle the main concern was summarized as follows:

“There is insufficient information to characterize the systemic exposure to miconazole from this product. Characterization of systemic exposure to miconazole is a component of the safety evaluation of this product.”

Additional items which were not non-approval (NA) issues are as follows:

- 1) An acceptable Tradename is needed in order to market this drug safely.
- 2) CMC issues remain outstanding (see CMC review).
- 3) Continued discussion of labeling is needed as the current version of labeling has not been entirely agreed upon. In addition will need to incorporate any new systemic exposure information submitted.
- 4) Additional clinical studies are recommended as per Dr. Carr, but not necessarily prior to approval. These studies are as follows:
  - a) The applicant should evaluate the safety and efficacy of their product in incontinent adults who have perineal dermatitis complicated by candidiasis.

- b) The applicant should assess repeated use of their product for relapse in pediatric patients.
  - c) The applicant should conduct a prospective study to assess for the development of drug resistance for the first year of marketing (a literature survey would not be sufficient).

A multidisciplinary review was conducted of the complete response to the NA letter dated August 15, 2006.

Systemic Exposure

The applicant addressed adequately concerns regarding systemic exposure and safety regarding hepatic adverse events in the current submission as reviewed in detail by the Clinical and Biopharmaceutics reviewers, Drs. Carr and Adebawale.

Non-NA Issues

- 1) An acceptable Tradename was submitted and reviewed by DMETS, DDMAC and the primary review team.
- 2) Outstanding CMC issues were resolved adequately and an approval recommendation was given as per Dr. Hathaway's review.

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- 3) Finalized labeling was discussed and agreed upon between Barrier and the Agency after several revisions.
- 4) Additional clinical study as described above was agreed upon to (b) and (c).

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The new submission provided an adequate response with regards to an update of safety for both this product and miconazole.

Approval Recommendation

In summary, it is recommended that the product VUSION Ointment (0.25% miconazole nitrate, 15% zinc oxide, and 81.35% white petrolatum) be approved for the indication of adjunctive treatment of diaper dermatitis only when complicated by documented candidiasis (microscopic evidence of pseudohyphae and/or budding yeasts), in immunocompetent pediatric patients 4 weeks and older.

Markham C. Luke, M.D., Ph.D.  
Lead Medical Officer, Dermatology

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/s/  
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Markham Luke  
2/16/2006 10:32:16 AM  
MEDICAL OFFICER  
Clinical TL memo regarding recommendation for action.

Stanka Kukich  
2/16/2006 03:10:06 PM  
MEDICAL OFFICER  
This regulatory action is based on a multidisciplinary review  
of the data in the NDA 21-026 and  
I concur with the recommendation that the Vusion  
Ointment be approved

**Clinical Team Leader Memorandum**

**NDA 21-026 AZ**

**Complete Response to Non-Approval Letter**

**TRADENAME Ointment**

**0.25% Miconazole Nitrate, 15% Zinc Oxide, and 81.35% White Petrolatum**

**May 23, 2005**

This memorandum is to address specific review issues regarding TRADENAME Ointment for the treatment of diaper dermatitis complicated by cutaneous candidiasis that need further description.

The primary medical reviewer, Dr. Brenda Carr, has carefully assessed the submission and recommends approval for this product in consultation with the other disciplines as per her completed review with a final revised date of May 16, 2005. However, a new informational piece emerged on May 18, 2005 during Dr. Carr's scheduled leave, that has impacted the approvability of this drug product.

As a result of the additional concerns, the team leader recommends that this product not be approved for marketing at this time, pending the review of additional data characterizing the extent of systemic exposure from the to-be-marketed formulation.

**Formulation and Pharmacokinetic Study Concern**

The primary chemistry reviewer, Dr. Saleh Turujman (see Chemistry, Manufacturing, and Controls or CMC review), informed the group that the product used in the pharmacokinetic (PK) bioavailability testing was not the final to-be-marketed drug product. The difference in formulation was that the specification for white petrolatum was different. The final to-be-marketed drug product uses white petrolatum, while the PK bioavailability testing used white petrolatum. The two petrolatums are sufficiently distinct (e.g. viscosity, look and feel) that a potential for differences in systemic exposure exists. Petrolatum, for this drug, is both a structure-forming excipient as well as an active ingredient.

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It was also not clear that the original PK studies were done in maximally exposed patients (i.e., infants with severe diaper dermatitis complicated by cutaneous candidiasis and under occlusion with diapers). The Clinical Pharmacology/Biopharmaceutics Team Leader informed the review team that this consideration results in a recommendation that "an additional in vivo biostudy be required prior to marketing."

The clinical team leader has significant safety concerns with regard to questions on systemic exposure with this product raised by the Clinical Pharmacology/Biopharmaceutics reviewers due to the relatively sparse pediatric clinical dataset presented in the pivotal clinical study. Safety monitoring in the clinical trials did not include laboratory monitoring that might have detected signals from systemic exposure. This product will be used in the smallest patients (infants) with broken skin and under occlusion, so systemic exposure is a safety concern.

In a teleconference on May 19, 2005, the Agency informed the applicant as to the above concern and the applicant stated that additional study information on the final to-be-marketed product that may address the systemic exposure for safety needs will be

forthcoming. However, upon review of the applicant's fax dated May 20, 2005, the additional information supports the contention that the two petrolatum specifications are different and provide different in vitro diffusion. The applicant indicated there was a "failure to show equivalency under SUPAC-SS under those studies [referring to in vitro diffusional studies]". However, the applicant points out that these studies were "designed to differentiate minute differences to various formulation and process parameters". Nonetheless, the ramifications for such differences for clinical systemic bioavailability and therefore systemic safety assessments were not made clear, nor are obvious.

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Given this concern, the clinical team leader recommends that a more thorough accounting for systemic exposure is needed prior to approval.

#### Labeling

It is expected that the majority of future use of this product will be in the pediatric population so consultation was obtained with the Division of Pediatric Drug Development. Dr. Lisa Mathis, the Acting Director, indicated via email that the following section: "TRADENAME Ointment should not be used as a substitute for frequent diaper changes. TRADENAME Ointment should not be used long term or to prevent the occurrence of diaper dermatitis, since long term or preventative use of an anti-microbial may result in the development of drug resistance." should also be included in the PRECAUTIONS: Pediatric Use section of labeling (package insert) for this product.

Additionally, the applicant proposed deletion of specific information in the Agency proposed INDICATIONS AND USAGE section and DOSAGE AND ADMINISTRATION section

Further discussions are needed regarding the sampling program. The applicant proposed both 5 g and 30 g samples be included in the package insert product information. The rationale and ramifications need to be further discussed with the applicant.

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#### Co-distribution and Tradename

The proposed tradename of Zimyca (Barrier) was deemed not recommended by the Division of Medication Errors and Technical Support (DMETS) in the Office of Drug Safety (see consult reply). The applicant has not submitted any other name in its place at this time.

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Conclusion

This product for diaper dermatitis in the setting of cutaneous candidiasis is not recommended for approval.

The remaining hurdle for approval of this product is as follows:

Sufficient information to support the systemic exposure of this product, given the unknown systemic safety consequences.

Additional items which are not non-approval (NA) issues are as follows:

- 1) An acceptable Tradename is needed in order to market this drug safely.
- 2) CMC issues remain outstanding (see CMC review).
- 3) Continued discussion of labeling is needed as the current version of labeling has not been entirely agreed upon. In addition will need to incorporate any new systemic exposure information submitted.
- 4) Additional clinical studies are recommended as per Dr. Carr, but not necessarily prior to approval. These studies are as follows:
  - a) The applicant should evaluate the safety and efficacy of their product in incontinent adults who have perineal dermatitis complicated by candidiasis.

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b) The applicant should assess repeated use of their product for relapse in pediatric patients.

c) The applicant should conduct a prospective study to assess for the development of drug resistance for the first year of marketing (a literature survey would not be sufficient).

Markham C. Luke, M.D., Ph.D.  
Lead Medical Officer, Dermatology

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/s/

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Markham Luke  
5/23/05 06:06:28 PM  
MEDICAL OFFICER  
NA recommendation

Jonathan Wilkin  
5/24/05 01:19:17 PM  
MEDICAL OFFICER

I concur that systemic exposure should be characterized for  
the to-be-marketed formulation as part of the overall  
safety assessment prior to approval.

## CLINICAL REVIEW 21-026

Application Type 505 (b)(2)  
Submission Number 000  
Submission Code AZ

Letter Date August 15, 2005  
Stamp Date August 16, 2005  
PDUFA Goal Date February 16, 2006

Reviewer Name Brenda Carr, M.D.  
Review Completion Date February 2, 2006

Established Name 0.25 % miconazole nitrate  
15% zinc oxide  
81.35% white petrolatum  
(Proposed) Trade Name Vusion™  
Therapeutic Classes antifungal (miconazole nitrate);  
skin protectants (zinc oxide and  
white petrolatum)  
Applicant Barrier Therapeutics, Inc.

Priority Designation S

Formulation ointment  
Dosing Regimen apply to affected area at each  
diaper change  
Indication for the adjunctive treatment of diaper  
dermatitis only when complicated by  
candidiasis, as documented by microscopic  
evidence of pseudohyphae and/or budding  
yeasts, in immunocompetent pediatric  
patients 4 weeks and older  
Intended Population pediatric patients 4 weeks and older

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Vusion (miconazole nitrate/zinc oxide/white petrolatum)

(i.e. hematologies and chemistries, including liver function testing). The study protocol should be submitted for review within two months of approval. The study start date should be within six months of approval. The final study report submission should be within 16 months of approval.

The applicant should conduct a prospective two-year longitudinal study to assess for development of miconazole resistance in *Candida* spp. following repeated treatment courses of topically applied 0.25% miconazole nitrate, 15% zinc oxide, and 81.35% white petrolatum ointment in infants with moderate to severe diaper dermatitis complicated by candidiasis. Clinical isolates of *Candida* spp should be obtained from patients who fail to improve with VUSTON™ Ointment treatment followed by properly conducted *in vitro* susceptibility testing. Isolates should be saved in the event that further studies of them are necessary. The study protocol should be submitted for review within four months of approval. The study protocol should be finalized within 12 months of approval. The study start date should be within 12 months of approval. The final study report submission should be six months after study completion and within three years of approval.

There are no recommendations for study of the product in premature infants or in older pediatric age groups.

### 1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests.

## 1.3 Summary of Clinical Findings

### 1.3.1 Brief Overview of Clinical Program

Data from the new Phase 3 trial, BT100 USA/100 (BT100) constitute the primary efficacy database. The applicant previously conducted three other Phase 3 trials, and those data were reviewed in previous submissions, one of which was the original submission of NDA 21-026 (submission date August 24, 1998).  
1985)

A primary deficiency for both applications was that the presence of infection by *Candida albicans* was not adequately established in study subjects at baseline. While cultures were collected at baseline and end-of-treatment in two of the three previous studies (no microbiological data were collected in the third study), microscopic testing for evidence of candidal infection (e.g. pseudohyphae) was not done. However, because those trials enrolled pediatric subjects with diaper dermatitis, some of whom cultured positive for *Candida albicans*, the Agency considered that some data could be extracted from the previously submitted trials that might be supportive of efficacy. Specifically, the clinical clearance data from the previous trials would be evaluated.

A total of 330 subjects were enrolled in BT100: 166 subjects were randomized to treatment with the applicant's product, and 164 subjects were randomized to treatment with zinc oxide/white petrolatum. Of the 330 subjects enrolled, 236 were included in the modified intent to-treat (MITT) population. Per the protocol, the MITT population was defined as all subjects

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## **1 EXECUTIVE SUMMARY**

### **1.1 Recommendation on Regulatory Action**

From a clinical perspective, it is recommended that the resubmission be approved for the adjunctive treatment of diaper dermatitis only when complicated by documented candidiasis (microscopic evidence of pseudohyphae and/or budding yeast), in immunocompetent pediatric patients 4 weeks and older. The applicant's product should be used as part of a treatment regimen that includes measures directed at the underlying diaper dermatitis, including gentle cleansing of the diaper area and frequent diaper changes. It is recommended that the product be available only by prescription.

The applicant's product, VUSION™, contains three active ingredients: 0.25% miconazole nitrate, 15% zinc oxide, and 81.35% white petrolatum. The applicant had previously provided information from the open public literature supporting the efficacy of both zinc oxide and white petrolatum in the treatment of diaper dermatitis. In this resubmission, the applicant provided information from the public domain supporting the safety of miconazole, including its use in the applicant's target pediatric populations.

The applicant had previously submitted clinical trial data which provided some evidence of the efficacy of this product. They also conducted one additional adequate and well-controlled study to demonstrate the superior effectiveness of the complete triad combination product over the dyad (zinc oxide and white petrolatum with inactive ingredients). Specifically, the applicant's triad combination product was superior to the zinc oxide/white petrolatum dyad in the treatment of diaper dermatitis complicated by candidiasis in patients up to 2 years of age. It is reasonable to extrapolate safety and efficacy to older pediatric age groups. Under conditions of study, the applicant's product was shown to be well-tolerated for its intended use. There are data to provide adequate direction for use of the product, although frequency of application and amount per application will vary from patient to patient, as the product is to be applied after each diaper change and the sizes of diaper areas vary according to the size of the child. Duration of treatment, however, is seven days.

### **1.2 Recommendation on Postmarketing Actions**

#### **1.2.1 Risk Management Activity**

There are no risk management activities recommended at this time.

#### **1.2.2 Required Phase 4 Commitments**

The applicant should conduct a study to assess the systemic absorption and safety of topically applied 0.25% miconazole nitrate, 15% zinc oxide, and 81.35% white petrolatum ointment in infants with moderate to severe diaper dermatitis complicated by candidiasis. The study should be conducted with the to-be-marketed formulation, and should include routine laboratory testing

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with confirmed *Candida spp.* who were dispensed study medication. Of the subjects included in the MITT population, 112 subjects received treatment with the applicant's product, and 124 subjects received treatment with zinc oxide/white petrolatum.

### 1.3.2 Efficacy

In study BT100, subjects were required to have positive KOH (pseudohyphae and/or budding yeast) and culture for *Candida spp.* and a Diaper Dermatitis Severity Index Score of 3-8 at baseline. The Diaper Dermatitis Severity Index Score was a global assessment that reflected erythema, papules or pustules and erosions. The primary endpoint in study BT100 was "Overall Cure" which required that subjects be assessed as both clinically cured (i.e. Diaper Dermatitis Severity Index Score of 0) and microbiologically eradicated at Day 14 (one week post-treatment).

The applicant's product was superior to zinc oxide/white petrolatum in the treatment of diaper dermatitis complicated by candidiasis in study BT100 in the last-observation-carried forward analysis. At Day 14, 23% of subjects treated with the applicant's product achieved "Overall Cure" compared to 10% of zinc oxide/white petrolatum-treated subjects. The applicant's product was also superior to zinc oxide/white petrolatum for the secondary endpoints "Clinical Cure" (38% versus 11%, respectively) and mycological cure at Day 14 (52% versus 29%, respectively). All of results were statistically significant. Efficacy was not demonstrated in subjects younger than 4 weeks.

In the supportive studies, when clinical clearing was considered for subjects who cultured positive for *Candida albicans* at baseline, the applicant's product trended towards superiority over zinc oxide/white petrolatum in one study and was superior to zinc oxide/white petrolatum in the other study. Assessment was at Day 7 in the supportive studies.

### 1.3.3 Safety

A total of 835 infants and young children were enrolled in the four Phase 3 studies, 418 of whom received treatment with the applicant's product, and 417 of whom received treatment with zinc oxide/white petrolatum. The duration of treatment was seven days in all of the studies, and application of study drug was at each diaper change. Only study BT100 included a post-treatment assessment (Day 14).

Adverse events were reported for 143 of the 835 subjects (17%) participating in the four Phase 3 studies: 58 of 418 subjects (14%) received treatment with the applicant's product, and 85 of 417 subjects (20%) received treatment with zinc oxide/white petrolatum. The most common adverse events were in the categories of infections and infestations (8% for the applicant's product, 12% for zinc oxide/white petrolatum), gastrointestinal disorders (2% for the applicant's product, 3% for zinc oxide/white petrolatum), and respiratory, thoracic and mediastinal disorders (3% for the applicant's product, 2% for zinc oxide/white petrolatum). One of 418 (0.2%) subjects treated with the applicant's product and two of 417 (0.5%) subjects treated with zinc oxide/white petrolatum experienced adverse events that may have been related to study treatment. There was no consistent difference in the occurrence of types of adverse events when the two treatment groups (the applicant's product and zinc oxide/white petrolatum) were compared.

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#### 1.3.4 Dosing Regimen and Administration

The product is to be applied to the diaper area at every diaper change, and the treatment duration is seven days. Dose-finding studies were not conducted.

#### 1.3.5 Drug-Drug Interactions

The applicant did not conduct drug-drug interaction studies. On February 28, 2001, the Center for Drug Evaluation and Research issued a Science Background statement regarding the safety of miconazole vaginal cream and suppositories. Specifically, the statement advised health care professionals that, "women who take a warfarin anticoagulant and use a miconazole intravaginal cream or suppository may be at risk for developing an increased prothrombin time, international normalized ratio (INR) and bleeding." The risk of this interaction with warfarin had been known following systemically administered miconazole. Labeling changes were recommended to advise consumers of this risk from use of the vaginal products. The pediatric patient population would generally appear to be at low risk for this interaction, since there is a low likelihood of pediatric subjects taking warfarin. However, some level of concern may still exist for individual patients and/or their caregivers.

#### 1.3.6 Special Populations

The primary patient population, infants and young children, is itself a special population, and use of the applicant's product was assessed in this group. Use of the product in the geriatric population (e.g. incontinent patients who are diapers wearers) has not been addressed.

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## 2 INTRODUCTION AND BACKGROUND

### 2.1 Product Information

The applicant's product contains three active ingredients: 0.25% miconazole nitrate, 15% zinc oxide, and 81.35% white petrolatum. The applicant's proposed indication is treatment of diaper dermatitis complicated by candidiasis.

Miconazole is an azole antifungal of the imidazole class. Other imidazole antifungals include ketocanazole, clotrimazole, econazole, and oxiconazole. Azoles are thought to inhibit fungal growth through impairment of biosynthesis of ergosterol, the primary sterol for the cytoplasmic membrane.<sup>1,2,3</sup> Azoles inhibit a cytochrome p-450-dependent enzyme, lanosterol 14 $\alpha$ -demethylase, resulting in the prevention of conversion of lanosterol into ergosterol. Ultimately, growth of fungal cells and permeability of fungal cell membranes are compromised.<sup>2,3</sup> Administration routes for imidazole antifungals include the oral, intravenous, topical, and intravaginal routes. Marketed formulations of miconazole include cream, spray, powder, and lotion products.<sup>1</sup> Topical azoles are reported as generally well-tolerated; however, irritation and burning are among the effects that have been reported.<sup>2</sup>

### 2.2 Currently Available Treatment for Indications

There are several products marketed over-the-counter for diaper rash; however, there is no prescription product marketed in the United States for this indication.

Diaper dermatitis is an umbrella diagnosis that speaks more to the location of an eruption than its etiology. The diagnosis may reflect an eruption that is coincidentally in the diaper area (e.g. seborrheic dermatitis) or an inflammatory process that is a function of conditions in the diaper environment. It is likely the latter category into which the diagnosis of "diaper dermatitis" most often falls, and it is a subset of this category that the applicant proposes to treat. In this review, "diaper dermatitis" refers to this latter category.

Skin wetness is thought to be a critical element in the pathogenesis of diaper dermatitis in at least two important ways: wet skin has an increased coefficient of friction and wet skin is more permeable, allowing for more ready penetration of irritants.<sup>4</sup> Friction and irritation play critical roles.<sup>5,6,7</sup> Causative and/or contributory factors may include moisture, urine pH, feces, proteolytic enzymes, soaps and detergents.<sup>5,6,7,8</sup> Infection by *Candida albicans* may secondarily complicate the underlying process and *Candida* may exacerbate the inflammation by the release of keratinases.<sup>8,9</sup> However, there is information suggesting that *Candida albicans* may play a primary role in causing some diaper dermatitis.<sup>7</sup>

At its core, treatment of diaper dermatitis requires strict attention to maintaining a clean, dry diaper environment. Gentle cleansing and frequent diaper changes are fundamental to this. Skin protectants, such as the zinc oxide and white petrolatum in the applicant's product, may be soothing and provide a barrier between the skin and the diaper contents. Some cases of diaper dermatitis may resolve with these measures alone. If the situation is complicated by candidiasis, an antifungal would be added to regimen.

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### 2.3 Availability of Proposed Active Ingredient in the United States

Miconazole nitrate is marketed in the United States in a variety of formulations. Indications include vulvovaginal candidiasis, tinea cruris, and tinea pedis. Dosing regimens and routes of administration vary (e.g. topical, intravaginal). Marketed concentrations of topical formulations include 2% and 4% strengths.

### 2.4 Important Issues With Pharmacologically Related Products

There are two classes of azole antifungal agents: the imidazoles and the triazoles. Most azoles under current development are reportedly of the triazole class primarily because:

- Systemic triazoles are metabolized more slowly.
- Systemic triazoles are said to have less effect on sterol synthesis in humans as compared to the imidazoles.<sup>9</sup>

The most common adverse reaction reported for azoles is gastrointestinal upset. Nausea and vomiting have been reported with systemically administered azoles. All azoles have reportedly been shown to cause liver enzyme abnormalities, and the potential for hepatotoxicity may be a significant concern.<sup>10,11</sup> Candidal resistance may emerge during prolonged treatment with azoles and is primarily limited to the immunosuppressed population. With *Candida albicans*, the primary mechanism for development of resistance is said to be accumulations of the gene that codes for the C14- $\alpha$ -sterol demethylase. Importantly, cross resistance is extended to all other azoles.<sup>1,12</sup>

### 2.5 Presubmission Regulatory Activity

The regulatory history surrounding the development of this product is long and complicated. In this review, discussion of the history will generally be limited to events that pertain to the resubmission dated November 24, 2004 on which a not-approvable action was taken on May 24, 2005. More detailed accounts of the regulatory history for this product can be found in the Medical Officers' reviews of previous submissions, including the resubmission dated November 24, 2004.

The not-approvable letter issued on May 24, 2005 cited the following deficiency:

"There is insufficient information to characterize the systemic exposure to miconazole from this product. Characterization of systemic exposure to miconazole is a component of the safety evaluation of the product."

The not-approvable action was based on the discovery, late in the review cycle, that the pharmacokinetic (PK) study was done with a formulation different from that proposed for marketing (and evaluated in Phase 3). Specifically, per the Executive Summary of the chemistry review dated May 23, 2005,

"The white petrolatum used in the PK study (Formulation F100) is the \_\_\_\_\_, which has a consistency of \_\_\_\_\_. The white petrolatum used in the clinical studies (Formulation F114) and in the to-be-marketed product is the \_\_\_\_\_ with a consistency of \_\_\_\_\_. The *in-vitro* release results of \_\_\_\_\_

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these two formulations (for miconazole), using the CDER SUPAC-SS Guidance, were found to be different."

As the release results from the *in vitro* studies differed, it could not be excluded that these differences might also be seen *in vivo*, possibly making for different extents of miconazole exposure from the two formulations. Thus, the extent to which the PK data collected from use of the earlier formulation might apply to the to-be-marketed formulation was unclear. There is no information regarding the extent of systemic exposure to miconazole from the to-be-marketed formulation. Further, routine laboratory testing was not done in the clinical development program, and results from such testing might have permitted some conclusions regarding systemic tolerance of the product [e.g. had laboratory testing revealed no signal of possible systemic effect(s)].

*Comment: Unless otherwise noted, in this review, references to "the applicant's product" refer to the to-be-marketed formulation.*

The not-approvable letter also advised that,

"When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level."

However, in the cover letter to the resubmission under current review, the applicant indicates that, "...we have no additional data from clinical or non-clinical studies, and...there have not been any significant changes or findings in the safety profile."

In an Information Request sent on May 31, 2005, the applicant was also requested to address the following clinical items in their resubmission:

"Additional clinical studies are recommended, but not necessarily prior to approval. These studies are as follows:

- a. The applicant should evaluate the safety and efficacy of their product in incontinent adults who have perineal dermatitis complicated by candidiasis.
- b. The applicant should assess repeated use of their product for relapse in pediatric patients.
- c. The applicant should conduct a prospective study to assess for the development of drug resistance for the first year of marketing (a literature survey would not be sufficient).
- d. Please conduct efficacy and safety evaluations of their product for diaper dermatitis complicated by cutaneous candidiasis in the under 4 week old group."

Pertaining to the above requests, in the cover letter to the resubmission, the applicant indicates that, "At this time, none of the other recommended studies seems appropriate or necessary."

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Late in the review cycle of the previous resubmission, it was discovered that the combination product used in this pharmacology study was not the to-be-marketed formulation (Please see Section 2.5 of the current review). The findings from this study are presented below, and the reviewer considers that they provide some relevant information regarding the absorption of miconazole from topically applied products under conditions of use similar to the applicant's product (i.e. at each diaper change for approximately seven days) and in a population similar to the target population for the applicant's product (i.e. infants). Blood samples for determination of miconazole levels were obtained before treatment on Day 1 and on Day 7. Routine laboratory testing (e.g. hematology and chemistries) was not done.

*Comment: It is noted that in the clinical pharmacology/ biopharmaceutics review dated April 21, 1999 also describes the Day 7 samples as being obtained prior to dosing on Day 7. Thus, it appears that the results from this study reflect six days of exposure to study products rather than exposure from a full treatment course of seven days.*

For subjects treated with the combination product used in this study (not the to-be-marketed formulation), the applicant reported that plasma concentrations were below the lower limit of detection (<1.0 ng/mL) for 15 of 18 infants (83%) and < 5 ng/mL for 3 of 18 infants (17%). Samples from one infant were reported to have been missing.

For subjects treated with 2% miconazole nitrate cream, plasma concentrations ranged from 5.2 to 7.4 ng/mL in four of the five infants (80%), and miconazole was below the lower limit of detection in one infant.

Pertaining to this study, in the review dated April 21, 1999, the clinical pharmacology/ biopharmaceutics reviewer concluded that,

"The applicant has demonstrated very low exposure of miconazole from the product on topical application."

*Comment: Data from the comparator of several fold higher concentration is also informative of absorption of miconazole from a topically applied product used in infants under conditions of use similar to those proposed for the applicant's product.*

*These values, seemingly reflecting six days of exposure to study products, are lower than those seen from a single dose of 200 mg miconazole nitrate cream applied topically to the vulvovaginal area and a single dose of 1200 mg administered intravaginally (Please see the discussion of NDA 20-968 in Section 7.1 of this review). The reviewer does not consider it likely that measurement of miconazole levels after seven days of usage (rather than six) would have made for substantially higher values, although after seven days of product usage would have been the more appropriate time-point for testing.*

*On October 18, 2005, the applicant submitted a protocol for a Phase 4 PK study to IND 21,542. The proposed study would be conducted in infants and with the to-be-marketed formulation. The study would include routine laboratory testing (hematology and chemistries, including liver function testing) at baseline and end of treatment.*

## 6 INTEGRATED REVIEW OF EFFICACY

The resubmission dated November 24, 2004 contained data from a new Phase 3 trial, BT100 USA/100. Those data constituted the primary efficacy database and were the focus of the

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Medical Officer's review of efficacy. Additionally, supportive efficacy data from previously-conducted Phase 3 trials were included. The efficacy findings are discussed in summary form below. Please see previous Medical Officer reviews, including the review dated May 18, 2005 (i.e. DFS entry date), for additional details regarding the efficacy findings from the applicant's clinical development program.

### **BT100 USA/100**

The Inclusion Criteria for Study BT100 USA/100 (BT100) specified enrollment of male and female neonates, infants, and children 2 through 4 years of age. Subjects were required to have positive KOH (pseudohyphae and/or budding yeast) and culture for *Candida spp.* and a Diaper Dermatitis Severity Index Score (see table below) of 3-8 at baseline. The Diaper Dermatitis Severity Index Score was a global assessment that reflected erythema, papules or pustules and erosions:

#### **Diaper Dermatitis Severity Index**

Score	Erythema	Papules or Pustules	Erosions
0	None to trace	None to trace	absent
1	Mild (pink)	Few (1-10)	present
2	Moderate (red)	Multiple (11-20)	NA
3	Severe (beefy red)	Many (21-40)	NA
4	NA	Abundant (>40)	NA

NA= not applicable

Subjects were randomized to treatment with either the applicant's triad product, miconazole nitrate/zinc oxide/white petrolatum, or treatment with a dyad product, zinc oxide/white petrolatum. Study drug was applied at each diaper change, and the duration of treatment was seven days. Subjects were evaluated at Day 0 (baseline), Day 3, Day 7 (end-of-treatment), and Day 14 (test-of-cure). The primary endpoint in study BT100, was "Overall Cure" which required that subjects be assessed at Day 14 (one week post-treatment) as both clinically cured (i.e. Diaper Dermatitis Severity Index Score of 0) and microbiologically eradicated.

### **Results**

A total of 330 subjects were enrolled in study BT100, and 166 subjects were randomized to treatment with the applicant's product, while 164 subjects were randomized to treatment with zinc oxide/white petrolatum. Of the 330 subjects enrolled, 236 were included in the modified intent-to-treat (MITT) population. Per the protocol, the MITT population was defined as all subjects with confirmed *Candida spp.* who were dispensed study medication. Of the subjects included in the MITT population, 112 subjects received treatment with the applicant's product, and 124 subjects received treatment with zinc oxide/white petrolatum.

The applicant's product was superior to zinc oxide/white petrolatum in the treatment of diaper dermatitis complicated by candidiasis. At Day 14, 26 of 112 of subjects (23%) treated with the applicant's product achieved "Overall Cure" compared to 12 of 124 subjects (10%) treated with zinc oxide/white petrolatum. The applicant's product was also superior to zinc oxide/white petrolatum for the secondary endpoints "Clinical Cure" (38% versus 11%, respectively) and

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mycological cure at Day 14 (52% versus 29%, respectively). All of results were statistically significant. Efficacy was not demonstrated in subjects younger than 4 weeks.

### Supportive Studies

The applicant had previously conducted three other Phase 3 trials, and those data were fully reviewed in two previous submissions, one of which was the original submission of NDA 21-026.

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A primary deficiency for both applications was that the presence of infection by *Candida albicans* was not established in study subjects at baseline. While cultures were collected at baseline and end-of-treatment in two of the three previous studies (no microbiological data were collected in the third study), microscopic testing for evidence of candidal infection (e.g. pseudohyphae) was not done. However, because those trials enrolled pediatric subjects with diaper dermatitis, some of whom cultured positive for *Candida albicans*, the Division considered that some data could be extracted that might be supportive of efficacy. Specifically, the clinical clearance data from the previous trials would be evaluated.

In the supportive studies, when clinical clearing was considered for subjects who cultured positive for *Candida albicans* at baseline, the applicant's product trended towards superiority over zinc oxide/white petrolatum in one study and was superior to zinc oxide/white petrolatum in the other study. Assessment was at Day 7 in the supportive studies. (Note: Microbiological data were not collected in the third study; therefore, this study was not designed to support the applicant's proposed indication and was not considered in the efficacy review.)

## **7 INTEGRATED REVIEW OF SAFETY**

### **7.1 Methods and Findings**

This review of safety will give an overview of the safety discussion found in the Medical Officer's review of the November 24, 2004 resubmission. Please see that review for additional details regarding the safety profile of the applicant's product. Additionally, the current review will summarize safety information from approved NDA's for miconazole products that was included in the resubmission dated August 15, 2005. The applicant references these applications as being supportive of the safety of their product.

#### **Safety Database from Applicant's Development Program**

A total of 835 infants and young children were enrolled in the four Phase 3 studies and constituted the safety database. Of the 835 subjects, 418 received treatment with the applicant's product, and 417 received zinc oxide/white petrolatum. The duration of treatment was seven days in all of the studies, and application of study drug was at each diaper change. Only study BT100 included a post-treatment assessment (Day 14).

Adverse events were reported for 143 of the 835 subjects (17%) participating in the four Phase 3 studies: 58 of 418 subjects (14%) received treatment with the applicant's product, and 85 of 417 subjects (20%) received treatment with zinc oxide/white petrolatum. The most

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common adverse events were in the categories of infections and infestations (8% for the applicant's product, 12% for zinc oxide/white petrolatum), gastrointestinal disorders (2% for the applicant's product, 3% for zinc oxide/white petrolatum), and respiratory, thoracic and mediastinal disorders (3% for the applicant's product, 2% for zinc oxide/white petrolatum). One of 418 (0.2%) subjects treated with the applicant's product and two of 417 (0.5%) subjects treated with zinc oxide/white petrolatum experienced adverse events that may have been related to study treatment. There was no consistent difference in the occurrence of types of adverse events when the two treatment groups (the applicant's product and zinc oxide/white petrolatum) were compared.

**Summary of Adverse Events-All Phase 3 studies at  $\geq 1\%$**

System Organ Class*	Applicant's Product N= 418	Zinc oxide/White petrolatum N=417
Number of Events Reported	78	110
Number of Subjects Reporting One or More Events	58	85 (20%)
Eye disorders	3 (1%)	1 (<1%)
Conjunctivitis	3 (1%)	1 (<1%)
Gastrointestinal	10 (2%)	14 (3%)
Diarrhoea	4 (1%)	9 (2%)
Loose stools	2 (<1%)	3 (1%)
General disorders and administration site conditions	9 (2%)	9 (2%)
Pyrexia	8 (2%)	9 (2%)
Infections and infestations	32 (8%)	52 (12%)
Bronchitis	2 (<1%)	3 (1%)
Candidiasis	3 (1%)	0 (0%)
Nasopharyngitis	8 (2%)	8 (2%)
Oral candidiasis	1 (<1%)	5 (1%)
Otitis media	3 (1%)	7 (2%)
Upper respiratory tract infection	5 (1%)	22 (5%)
Respiratory, thoracic and mediastinal disorders	11 (3%)	7 (2%)
Cough	5 (1%)	0 (0%)
Nasal congestion	3 (1%)	1 (<1%)
Rhinorrhoea	2 (<1%)	4 (1%)

Total number of events in the system organ class; specific events are only reported if they occurred at  $\geq 1\%$ .

**Supportive Safety Information Submitted by Applicant (from approved NDA's)**

Subsequent to the not-approvable action dated May 24, 2005, the applicant was requested to provide information regarding the possible effects of miconazole on the liver, particularly in infants. The basis for this request is that miconazole is an azole antifungal (imidazole class), and azoles have been shown to cause liver enzyme abnormalities, and the potential for hepatotoxicity may be a significant concern.<sup>10,11</sup> Routine laboratory testing was not done in the applicant's development program.

In the resubmission under current review, to address the issue of hepatotoxicity associated with use of miconazole, the applicant cited safety data that the Agency relied on for approval of other miconazole dosage forms. Additionally, the applicant submitted literature reports of use of miconazole in pediatric subjects. (Please see Section 7.2.2.3 of the review for discussion of the literature reports).

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NDA 17-450 (submission date: March 2, 1973; approval letter issued January 30, 1974)

The applicant provided the Summary of Basis of Approval for this NDA (document dated November 13, 1973). This application proposed use of miconazole nitrate 2% vaginal cream for treatment of vulvovaginal candidiasis. In the summary, the Medical Officer states that, "Safety was demonstrated in extensive animal and human testing which revealed the drug to be well tolerated. No significant drug related biochemical or physical abnormalities were detected." There was no additional discussion of results of clinical safety testing in the summary. It is also noted that in the summary, the pharmacology reviewer states, "The liver seems to be the principal target organ for miconazole toxicity, mild degenerative hepatic changes being seen in both rats and dogs treated on a chronic basis."

*Comment: That no "significant" drug-related laboratory abnormalities were detected implies that drug-related laboratory abnormalities might have been observed. However, laboratory findings were not otherwise discussed in the summary.*

NDA 17-494 (submission date: May 7, 1973)

The applicant provided the Medical Officer's Summary of the NDA in the resubmission. This application initially proposed use of 2% miconazole nitrate cream for treatment of dermatophytosis, moniliasis and gram positive bacterial infections.

Per the Medical Officer's summary, laboratory tests were performed in four of the "clinical efficacy" trials. In one trial, adult males with tinea pedis received treatment with miconazole or vehicle cream twice daily for 28 days. "Serial" laboratory tests were performed through day 56 on 9 miconazole-treated subjects and 9 vehicle-treated subjects (frequency of testing was not specified). Pertaining to testing of liver function, increased SGOT was noted at days 28 and 56 in one miconazole-treated subject. The reviewer stated that lab results were otherwise "comparable to pre-treatment values or were abnormalities occurring after cessation of treatment" (Note: Specific lab values were not included in the discussion of any of the studies).

In two other studies, described collectively in the submitted summary, subjects with "tinea pedis, cruris and corporis" were treated with miconazole or vehicle cream twice daily for 28 days. Laboratory testing was done "initially" and at day 28 in 12 miconazole-treated subjects and 14 vehicle-treated subjects. Pertaining to testing of liver function, increased SGPT was noted at day 28 for two subjects in each treatment group. Results were otherwise "comparable to pre-treatment values."

In a fourth study of bilateral paired comparison design, adult males with tinea pedis received miconazole treatment to one foot (treatment of the other foot was not specified). In the summary, the Medical Officer indicated that frequency and duration of treatment were not stated. "Serial" laboratory testing was done through day 56 on 13 subjects. A "slightly increased AP" was reported at days 28 and 56 in one subject.

In a subtotal innocuous safety study, 10 subjects were treated with miconazole cream and 5 with placebo cream twice daily for 28 days. At each application, 2.5 gm of study product was applied to the entire back. Results of "serial" laboratory testing were said to be generally

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comparable to pre-treatment values; however, increased SGOT was noted in two subjects in the miconazole group and one subject in the placebo group.

The reviewer also described "additional clinical studies, performed in Europe," and these studies, described in "summary form" included

- Eight studies (described collectively) on oral use of miconazole in approximately 150 subjects with systemic candidiasis, 64 of whom had laboratory testing done. Dosages ranged from 250 mg to 3 gm per day for treatment durations of 2 to 9 weeks. No "drug-related" changes were found in any laboratory parameters.
- Three studies (also described collectively) were reported on the intravenous administration of miconazole in 9 subjects with "systemic mycoses or preterminal carcinoma." Dosages were 20 mg BID-TID for 7-10 days in 3 subjects and 600 daily BIW or TIW for a total of 14 infusions in 6 subjects. Liver and renal function tests were done in 3 subjects, and no "drug-related" changes were found in any laboratory parameters.

*Comment: Pertaining to the European studies, that there were no reports of drug-related changes in laboratory results, suggests that changes of some sort might have been seen in laboratory parameters. If there were changes noted in the laboratory results, it was not described how the changes were assessed as not being "drug-related." No additional information was provided regarding laboratory testing.*

The Medical Officer concluded that the product was safe for the proposed usage.

#### NDA 18-040

The applicant submitted a Medical Officer review that appears to be of the "original" NDA, the submission date of which was listed as May 24, 1977. This application proposed miconazole (10 mg/ml) for intravenous and intrathecal administration, and for bladder irrigation. While the proposed indications were not found to have been expressly stated, the clinical trials evaluated use of the product in various fungal infections (coccidiomycosis, systemic candidosis, urinary tract candidosis, mucocutaneous candidosis, cryptococcosis, paracoccidioidomycosis, and fungal meningitis).

Use of this product was evaluated in adult and pediatric subjects. Pediatric subjects were said to have tolerated doses of up to 65 mg/kg/day and up to 15/mg/kg (frequency of the latter dosage was not stated). No other information was presented regarding dosing in pediatric subjects, e.g. duration(s) of treatment. While the numbers and ages of the pediatric subjects were not provided, the reviewer stated that, "There is no adequate information on the use of the drug in children under one year."

Adverse events were discussed in general and not according to their occurrence in adult versus pediatric subjects. In the discussion of safety, the reviewer states, "Most patients undergoing Monistat I.V. treatment had severely debilitating underlying conditions...some were cachectic and/or moribund at the onset of the Monistat I.V. treatment. Thus, it is difficult to arrive at precise statements regarding the incidence of adverse effects caused by Monistat I.V." However, the reviewer reported that, "No adverse effects on bone marrow, and renal functions and on biochemical parameters of liver functions were reported."

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The review also discusses the results from a clinical pharmacology study in which four normal adults each received an infusion of 522 mg of miconazole. The average plasma concentrations at 15, 60 and 240 minutes were 6.18, 1.90 and 0.44 µg, respectively.

The Medical Officer ultimately concluded that "Monistat I.V is a safe drug within the limits of the package insert...amended according to this review" (that package insert was not found in the resubmission).

NDA 20-968 (submission date: June 30, 1998)

This application proposed single-dose use of miconazole 1200 mg soft gel vaginal insert and 2% miconazole external vulvar cream (frequency and duration of use of the cream was unclear) for intravaginal and topical use, respectively for treatment of vulvovaginal candidiasis. The clinical trials enrolled adult females.

The application included a drug absorption study of miconazole nitrate in normal female volunteers which evaluated the safety and drug absorption of miconazole from a miconazole nitrate vaginal ovule. Subjects received either a single dose of 1200 mg or a first dose of 1200 mg followed by a second 1200 mg dose 48 hours later (to represent a misuse scenario). Hematology, biochemistry and urinalysis were done at study admission and prior to study discharge, and this was the only study in the application that included routine laboratory testing. Mean  $C_{max}$  for a single dose was 10.7 ng/ml, and the levels attained were reported to be within the range of those obtained with 200 mg miconazole nitrate cream (9.48 - 12.68 ng/ml). Mean  $C_{max}$  for the twice-dosed group was 11.98 ng/ml, and also reported to be comparable to the levels seen with 200 mg cream. "The results of hematology, chemistry, and urinalysis studies were either within normal limits or judged by an investigator to be not clinically significant."

*Comment: The data in the referenced NDA's were considered adequate to support the safety of miconazole in the populations studied and for the indications proposed, as they were relied on by the Agency to support approval. However, since most of the information pertains to use of miconazole in adults, the extent to which it might be considered supportive of safety of the substance in the applicant's target pediatric population is unclear. Also, the numbers of subjects studied who had laboratory testing done were generally small.*

*It is not clear to what extent data from subjects treated for tinea pedis might compare to those from treatment in the diaper area (NDA 17-494). While both areas might be considered occluded, the extent of absorption from the two areas might differ for reasons which include the difference in the thickness of the stratum corneum. Additionally, surface areas might differ. However, subjects with tinea pedis did receive longer exposures to a higher concentration miconazole product than is proposed for treatment of diaper dermatitis complicated by candidiasis.*

*Pediatric subjects were evaluated in clinical trials conducted to support NDA 18-040 in which miconazole (10 mg/ml) was evaluated for intravenous and intrathecal administration, and for bladder irrigation for treatment of various fungal infections. Miconazole exposures would likely have been highest in this application because of the routes of administration. However, the paucity of details specifically pertaining to the pediatric subjects permits only limited conclusions regarding their tolerance of study drug. Numbers and ages of pediatric subjects were not described, nor were complete specifics of the dosing regimens, e.g. durations of treatment, routes of administration. Additionally, the Medical Officer's review stated that,*

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*"There (was) no adequate information on the use of the drug in children under one year." As a portion of the target population for the applicant's product would fall into this category, adequate safety information is needed to support use of the product in this age group. The risk/benefit assessment for treatment of systemic fungal infections would differ from that for treatment of diaper dermatitis complicated by candidiasis. Of note, however, is that the reviewer reported that "no" adverse effects were reported for laboratory parameters (hematologies and chemistries). While not specifically cited, this blanket statement is presumed to be inclusive of the pediatric subjects.*

*Pertaining to NDA 20-968, the miconazole levels obtained following a single dose of 200 mg miconazole nitrate cream applied topically to the vulvovaginal area and a single dose of 1200 mg applied intravaginally were higher than the levels in infants following six days of exposure to 0.25% or 2% miconazole containing products (Please see discussion of the applicant's PK study conducted in infants Section 5.1 of this review; however, the to-be-marketed formulation was not evaluated in this study. Also, please see required Phase 4 commitments in Section 9.3.2).*

#### 7.2.2.3 Literature

The applicant also included literature references which they believe support the safety of miconazole in pediatric subjects:

Thomas J. Fischer et al., Miconazole in the Treatment of Chronic Mucocutaneous Candidiasis: A Preliminary Report, J. Pediatr, 91(5), 815-19 (Nov. 1977).

The authors treated 5 hospitalized pediatric patients who had chronic mucocutaneous candidiasis with intravenous miconazole (supplied as 10 mg/ml). All subjects had been unresponsive to topical and oral antifungal therapy or had required repeated courses of amphotericin B. Two of the 5 subjects were in the age range relevant to the applicant's proposed target population: a 1 ½-year-old female and a 2 ½-year-old male. Miconazole dosages were 10 and 17 mg/kg/dose, respectively, with total doses of 2,295 mg (over 10 days) and 2,000 mg (over 3 days). The serum miconazole concentrations at 7 hours were 0.25 µg/ml and 0.33 µg/ml for the younger and older subjects, respectively (the 1 hour level, provided only for the 1 ½ year old, was 1.6 µg/ml). Adverse effects for the 1 ½-year-old subject were fever and anemia. Adverse effects for the 2 ½-year-old subject were fever, phlebitis and pruritus. Neither subject was reported to have had elevations of transaminases; however, it appears that the older subject may not have had repeat testing of liver enzymes.

Two older subjects, an 8-year-old male and a 16-year-old female, received additional treatment with weekly intravenous doses of miconazole (400 mg and 800 mg, respectively) for 15 months. Both subjects who received extended treatment (15 months) demonstrated elevated SGOT and SGPT levels. Date(s) of laboratory testing (i.e. relative to duration of exposure) were not provided.

G.J. Barton et al., Monitored Release of Intravenous Miconazole in the United Kingdom. A Report of the First 2 Years Experience, 28, 33, in The Role of Miconazole in the Treatment of Systemic Mycoses: Royal Society of Medicine International Congress and Symposium Series No. 45

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The authors reviewed 121 hospital case record forms for patients treated with intravenous miconazole for systemic mycoses. Twelve patients were under 5 years of age, 3 of whom were pre-term infants (one subject was 5 weeks old; no information was found regarding the ages of the other 11 subjects). Two of the pre-term infants presented with *Candida*-positive blood cultures and were treated with 20 mg/kg/day (duration not stated). Seven of the pediatric patients under 5 years of age were treated for candidosis. Mean dose of intravenous-administered miconazole was provided for all 121 patients (i.e. not separately for pediatric subjects) and was 1474 mg/day. "Serum biochemistry and haematology examinations were made in 108 patients and no significant drug-related changes were reported. None of the records received indicated renal or hepatic toxicity after i.v. miconazole."

*Comment: It is unclear how many (if any) of the 12 subjects younger than 5 years of age were among the 108 who had laboratory testing done. That no "significant" drug-related changes were reported for hematologic and chemistry parameters does not preclude the occurrence of any drug-related effects.*

Ziad M. Shehab et al., Imidazole Therapy of Coccidioidal Meningitis in Children, *Pediat. Infect. Dis. J.* 7:40-44 (Jan. 1988).

The authors reported on nine children with coccidioidal meningitis, eight of whom were treated with orally-administered ketoconazole and intraventricularly-administered miconazole. Four of the subjects had previously been treated with amphotericin B with "severe" toxicity in all. Five subjects were younger than 3 years of age (the youngest was 19 months). Miconazole (3-5 mg) was administered daily initially then tapered to once weekly within the first 2 to 6 months, with subsequent tapering (based on treatment response) to once every other week then every third and fourth week before being discontinued. Duration of miconazole therapy ranged from 12 to 79 months. "There was no evidence of hepatic toxicity." "The liver enzyme levels (alanine aminotransferase and aspartate aminotransferase) remain within normal limits except for an occasional rise to less than twice the normal values." Frequency of testing not provided.

*Comment: Dosages and durations of treatment would far exceed proposed conditions of use for the applicant's product. That there was no evidence of hepatic toxicity might be supportive of safety of miconazole, since most subjects were also receiving ketoconazole, also known to potentially cause hepatotoxicity. However, the extent of systemic exposure and potential for toxicity from intraventricularly-administered miconazole is unclear, and this report might be more reflective of the safety of ketoconazole.*

U.B. Schaad et al., Pilot Study Comparing Miconazole Gel and Nystatin Suspension in the Therapy of Oral Thrush, 5-6, 15 [Translated from original (German) published in *Schweiz. Med. Wschr.*, 113(38); 1356-62 (1983)].

In this study miconazole gel and nystatin suspension were compared in 42 hospitalized, pediatric subjects with oral candidiasis. Dosages were 100 mg per day of miconazole for subjects < 10 kg and 200 mg per day in subjects > 10 kg (divided dosages four times per day). Duration of dosing was unclear. Laboratory testing (hematogram, urinalysis, GOT GPT and creatinine) was done in 12 infants up to 4 weeks of age (8 miconazole-treated, 4 nystatin). Time-

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point(s) of laboratory testing was unclear. The authors reported, "...laboratory examinations before and after therapy did not point to any blood cell, kidney or liver toxicity."

E.B. Larbi, et al., A Randomized, Double-blind, Clinical Trial of Topical Clotrimazole versus Miconazole for Treatment of Cutaneous Leishmaniasis in the Eastern Province of Saudi Arabia. Am J Top. Med. Hyg.; 52(2),1995, pp166-168.

This study enrolled adults and children. Either miconazole cream 2% or clotrimazole cream 1% were applied to lesions twice daily for 30 consecutive days, and subjects were to treat all of their lesions. Extent of exposure would therefore have varied as the numbers and sizes of lesions varied from patient to patient. Labs were obtained at baseline and at the end of treatment and included liver function tests. While the number of pediatric subjects was not provided, the youngest subjects were 2 years old in the miconazole group and 1 year old in the clotrimazole group. The authors reported, "There was no significant difference between the results of the pretreatment and post-treatment biochemical, hematologic, and radiologic investigations." (It is unclear whether this comparison is between treatment groups or between pre and post treatment labs within a treatment group)

#### 7.2.8 Assessment of Quality and Completeness of Data

The applicant provided information from approved NDA's and from the literature regarding tolerance of miconazole when given at a variety of doses, administered by different routes, in various patient populations and for a variety of indications. Much of the information did not specifically pertain to the applicant's target pediatric populations, and for those studies that did include pediatric subjects, helpful details were sometimes lacking, e.g. the numbers of pediatric subjects and their ages, specifics of dosing regimens. Also, the numbers of subjects per study in whom laboratory testing was done were often small, and it was not always clear if pediatric subjects were among those who had laboratory testing done. However, broad summary statements that were offered regarding tolerance of miconazole in both the cited NDA's and the literature references appear to support safety of miconazole (under the conditions of use and in the populations studied in the cited supportive information, including pediatric subjects). In the aggregate, the provided information suggests that the risk of hepatotoxicity from use of miconazole may be low and that clinically significant liver effects may not be a frequent finding.

At 0.25%, the concentration of miconazole in the applicant's product is less than in the miconazole products used in the cited NDA's and literature references. Dosing in some of the supportive information provided by the applicant (e.g. routes of administration, dosage amount), would almost certainly potentially make for systemic exposures in excess of those that might be obtained from the topical application of the applicant's 0.25% miconazole product used for a seven day period even if usage is under occlusion. Topical administration could further limit the potential extent of systemic exposure, as according to the clinical pharmacology/biopharmaceutics review dated April 21, 1999, "The absorption of miconazole from various topical formulations because of percutaneous absorption in adults is minimal." Although, it is unclear to what extent the adult data might apply to the target pediatric populations, data from the applicant's PK study conducted in infants under conditions similar to proposed use, suggest low percutaneous absorption through infant skin (the to-be-marketed formulation was not evaluated in this study). This PK study compared miconazole absorption from products of

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0.25% and 2% concentrations. Although this PK study was not conducted with the to-be-marketed formulation, the results suggest minimal absorption of topically applied miconazole products (including the 2% concentration) under similar conditions of use as for the applicant's product. However, routine laboratory testing was not done, so there was no assessment for possible laboratory effects from those amounts of miconazole that were absorbed.

Although limited, the applicant has provided information that appears to support the safety of miconazole in pediatric subjects. Some of the information is from exposures to systemically administered, higher concentrations than the applicant's product and for treatment durations longer than what the applicant proposes for their product.

## 7.2.9 Additional Submissions, Including Safety Update

The not-approvable letter advised that the complete response should include a safety update. In the cover letter to the submission, the applicant addresses the request for a safety update stating that, "...we have no additional data from clinical or non-clinical studies, and that there have not been any significant changes or findings in the safety profile."

## 8 ADDITIONAL CLINICAL ISSUES

### 8.8 Other Relevant Materials

In a consult response with signature date September 15, 2005, the Division of Medical Errors and Technical Support (DMETS) offered the following (full consult is in DFS),

"DMETS has no objections to the use of the proprietary name, Vusion from a safety perspective. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document."

Division of Drug Risk Evaluation (DDRE), was requested to look at the AERS database for hepatotoxicity/hepatic events for the miconazole topical and suppository dosage forms(full consult is in DFS):

"(A) search in the AERS system starting Dec 28, 05 resulted in total of seven cases after all exclusions..."

- 1) "Five out of the seven cases were confounded by one or more factors listed below.
- 2) "Monistat lotion was used orally in one case, monistat cream was used in 2 cases, monistat vaginal tablets was used in one case, miconazole ointment (Daktarin®) was used in one of the cases. Two cases did not indicate the form of miconazole or the route of administration.
- 3) "Five cases were confounded by multiple of concomitant systemic medications that can play a role in hepatic event.
- 4) "One case, an AIDS patient had a preexisting liver condition including hepatitis B & C and liver cirrhosis.
- 5) "One case was associated Alcohol abuse and possible drug abuse or overdose.
- 6) "There were only two relevant cases where topical use of miconazole cream may have resulted in hepatitis. One of those cases was reported in the literature. Both of those cases were strengthened by positive dechallenge and rechallenge. One of the cases did not provide information regarding past medical history or concomitant medication."

Clinical Review  
Brenda Carr, M.D.  
NDA 21-026-000  
Vusion (miconazole nitrate/zinc oxide/white petrolatum)  
The DDRE reviewer concluded,

"Base on these cases, I don't see a strong association between topical use of miconazole nitrate and hepatic adverse events."

## 9 OVERALL ASSESSMENT

### 9.1 Conclusions

The applicant provided information from approved NDA's and from the literature regarding tolerance of miconazole when given at a variety of doses, administered by different routes, in various patient populations, and for a variety of indications. Much of the information did not specifically pertain to the applicant's target pediatric populations, and for those studies that did include pediatric subjects, helpful details were sometimes lacking, e.g. the numbers of pediatric subjects and their ages, specifics of dosing regimens. Also, the numbers of subjects per study in whom laboratory testing was done were often small, and it was not always clear if pediatric subjects were among those who had laboratory testing done. However, broad summary statements that were offered regarding tolerance of miconazole in both the cited NDA's and the literature references appear to support safety of miconazole (under the conditions of use and in the populations studied in the cited supportive information, including pediatric subjects). In the aggregate, the provided information suggests that the risk of hepatotoxicity from use of miconazole may be low and that clinically significant liver effects may not be a frequent finding.

At 0.25%, the concentration of miconazole in the applicant's product is less than in the miconazole products in the cited NDA's and literature references. Dosing in some of the supportive information provided by the applicant (e.g. routes of administration, dosage amount), would almost certainly potentially make for systemic exposures in excess of those that might be obtained from the topical application of the applicant's 0.25% miconazole product used for a seven day period even if usage is under occlusion. Topical administration could further limit the potential extent of systemic exposure, as according to the clinical pharmacology/biopharmaceutics review dated April 21, 1999, "The absorption of miconazole from various topical formulations because of percutaneous absorption in adults is minimal." Although, it is unclear to what extent the adult data might apply to the target pediatric populations, data from the applicant's PK study conducted in infants under conditions similar to proposed use, suggest low percutaneous absorption through infant skin (the to-be-marketed formulation was not evaluated in this study). This PK study compared miconazole absorption from products of 0.25% and 2% concentrations. Although this PK study was not conducted with the to-be-marketed formulation, the results suggest minimal absorption of topically applied miconazole products (including the 2% concentration) under similar conditions of use as for the applicant's product. However, routine laboratory testing was not done, so there was no assessment for possible laboratory effects from those amounts of miconazole that were absorbed.

Although limited, the applicant has provided information that appears to support the safety of miconazole in pediatric subjects. Some of the information is from exposures to systemically administered, higher concentrations than the applicant's product and for treatment durations longer than what the applicant proposes for their product.

Clinical Review  
Brenda Carr, M.D.  
NDA 21-026-000  
Vusion (miconazole nitrate/zinc oxide/white petrolatum)

## 9.2 Recommendation on Regulatory Action

From a clinical perspective, it is recommended that the resubmission be approved for the adjunctive treatment of diaper dermatitis only when complicated by documented candidiasis (microscopic evidence of pseudohyphae and/or budding yeast), in immunocompetent pediatric patients 4 weeks and older. The applicant's product should be used as part of a treatment regimen that includes measures directed at the underlying diaper dermatitis, including gentle cleansing of the diaper area and frequent diaper changes. It is recommended that the product be available only by prescription.

## 9.3 Recommendation on Postmarketing Actions

### 9.3.1 Risk Management Activity

There are no risk management activities recommended at this time.

### 9.3.2 Required Phase 4 Commitments

The applicant should conduct a study to assess the systemic absorption and safety of topically applied 0.25% miconazole nitrate, 15% zinc oxide, and 81.35% white petrolatum ointment in infants with moderate to severe diaper dermatitis complicated by candidiasis. The study should be conducted with the to-be-marketed formulation, and should include routine laboratory testing (i.e. hematologies and chemistries, including liver function testing). The study protocol should be submitted for review within two months of approval. The study start date should be within six months of approval. The final study report submission should be within 16 months of approval.

The applicant should conduct a prospective two-year longitudinal study to assess for development of miconazole resistance in *Candida* spp. following repeated treatment courses of topically applied 0.25% miconazole nitrate, 15% zinc oxide, and 81.35% white petrolatum ointment in infants with moderate to severe diaper dermatitis complicated by candidiasis (Please see Section 2.4 of this review). Clinical isolates of *Candida* spp should be obtained from patients who fail to improve with VUSION™ Ointment treatment followed by properly conducted *in vitro* susceptibility testing. Isolates should be saved in the event that further studies of them are necessary. The study protocol should be submitted for review within four months of approval. The study protocol should be finalized within 12 months of approval. The study start date should be within 12 months of approval. The final study report submission should be six months after study completion and within three years of approval.

There are no recommendations for study of the product in premature infants or in older pediatric age groups.

### 9.3.3 Other Phase 4 Requests

There are no other Phase 4 requests.

13 Page(s) Withheld

           Trade Secret / Confidential

  2   Draft Labeling

           Deliberative Process

Clinical Review

Brenda Carr, M.D.

NDA 21-026-000

Vusion (miconazole nitrate/zinc oxide/white petrolatum)

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/s/

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Brenda Carr  
2/8/2006 03:17:06 PM  
MEDICAL OFFICER

Markham Luke  
2/8/2006 03:25:04 PM  
MEDICAL OFFICER  
Concur with Dr. Carr with regard to approval recommendation.

Stanka Kukich  
2/15/2006 05:53:44 PM  
MEDICAL OFFICER

## CLINICAL REVIEW

Application Type	505(b)(2)
Submission Number	21-026
Submission Code	AZ
Letter Date	November 24, 2004
Stamp Date	November 24, 2004
PDUFA Goal Date	May 24, 2005
Reviewer Name	Brenda Carr, M.D.
Review Completion Date	May 2, 2005; revised May 16, 2005
Established Name	0.25 % miconazole nitrate 15% zinc oxide 81.35% white petrolatum
(Proposed) Trade Name	Zimycan
Therapeutic Class	antifungal (miconazole nitrate) skin protectants (zinc oxide and white petrolatum)
Applicant	Barrier Therapeutics, Inc.
Priority Designation	S
Formulation	ointment
Dosing Regimen	apply to affected area at each diaper change
Indication	treatment of diaper dermatitis complicated by candidiasis
Intended Population	pediatric patients 4 weeks and older

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## 1 Executive Summary

### 1.1 Recommendation on Regulatory Action

From a clinical perspective, it is recommended that the resubmission be approved for treatment of diaper dermatitis complicated by candidiasis in pediatric patients 4 weeks and older. It is recommended that the product be available only by prescription.

The applicant's product contains three active ingredients: miconazole nitrate, zinc oxide and white petrolatum. The sponsor provided evidence already available in the open public literature suggesting the efficacy of both zinc oxide and white petrolatum in the treatment of diaper dermatitis. Since the applicant had previously submitted clinical trial data which provided supportive evidence for this product, the applicant conducted one adequate and well-controlled study to demonstrate the superior effectiveness of the complete triad combination product over the dyad (zinc oxide and white petrolatum with inactive ingredients) in support of this submission. The applicant's triad combination product was superior to the zinc oxide/white petrolatum dyad in the treatment of diaper dermatitis complicated by candidiasis in patients up to 2 years of age. It is reasonable to extrapolate safety and efficacy to older pediatric age groups. The applicant's product was also shown to be well-tolerated for its intended use.

There are data to provide adequate direction for use, although frequency of application and amount per application will vary from patient to patient, as the product is to be applied after each diaper change and the sizes of diaper areas vary according to the size of the child. Duration of treatment, however, is seven days.

### 1.2 Recommendation on Postmarketing Actions

#### 1.2.1 Risk Management Activity

There are no risk management activities recommended at this time.

#### 1.2.2 Required Phase 4 Commitments

The applicant should evaluate the safety and efficacy of their product in incontinent adults who have perineal dermatitis complicated by candidiasis. Long-term safety will need to be addressed in this older population as there may be greater potential for chronic use. Additionally, because of the potential for chronic use in the older population, heightened concerns may exist regarding the potential for development of resistance. The applicant will need to adequately address 300.50 for the perineal dermatitis indication.

The applicant should assess repeated use of their product for relapse in pediatric patients. There are no recommendations for study of the product in premature infants or in older pediatric age groups.

The applicant should conduct a study to assess for the development of drug resistance for the first year of marketing (a literature survey would not be sufficient). The quality and outcome of this study would serve as the basis for reconsidering the appropriateness of the applicant's proposal to provide samples of their product.

It is recommended that the protocols for all of the Phase 4 studies be submitted by December 2005 and that the recommended studies be conducted within two years of submission of the protocols. The study reports should be submitted six months following completion of the study.

### 1.2.3 Other Phase 4 Requests

There are no Phase 4 requests.

## 1.3 Summary of Clinical Findings

### 1.3.1 Brief Overview of Clinical Program

The re-submission contained data from a new Phase 3 trial, BT100 USA/100 (BT100), and those data constitute the primary efficacy database and are the primary focus of this review. The applicant previously conducted three other Phase 3 trials, and those data were reviewed in two previous submissions, one of which was the original submission of NDA 21-026.

A primary deficiency for both applications was that the presence of infection by *Candida albicans* was not adequately established in study subjects at baseline. While cultures were collected at baseline and end-of-treatment in two of the three previous studies (no microbiological data were collected in the third study), microscopic testing for evidence of candidal infection (e.g. pseudohyphae) was not done. However, because those trials enrolled pediatric subjects with diaper dermatitis, some of whom cultured positive for *Candida albicans*, the Agency considered that some data could be extracted from the previously submitted trials that might be supportive of efficacy. Specifically, the clinical clearance data from the previous trials would be evaluated.

A total of 330 subjects were enrolled in BT100, 166 subjects were randomized to treatment with the applicant's product, and 164 subjects were randomized to treatment with zinc oxide/white petrolatum. Of the 330 subjects enrolled, 236 were included in the modified intent-to-treat (MITT) population. Per the protocol, the MITT population was defined as "all subjects with confirmed *Candida spp.* who were dispensed study medication (active or vehicle)." Of the subjects included in the MITT population, 112 subjects received treatment with the applicant's product, and 124 subjects received treatment with zinc oxide/white petrolatum.

### 1.3.2 Efficacy

In study BT100, subjects were required to have positive KOH (pseudohyphae and/or budding yeast) and culture for *Candida spp.* and a Diaper Dermatitis Severity Index Score of 3-8 at baseline. The Diaper Dermatitis Severity Index Score was a global assessment that reflected erythema, papules or pustules and erosions. The primary endpoint in the new study, BT100, was "Overall Cure" which required that subjects be assessed at Day 14 (one week post-treatment) as both clinically cured (i.e. Diaper Dermatitis Severity Index Score of 0) and microbiologically eradicated.

The applicant's product was superior to zinc oxide/white petrolatum in the treatment of diaper dermatitis complicated by candidiasis in study BT100 in the last-observation-carried forward

analysis. At Day 14, 23% of subjects treated with the applicant's product achieved "Overall Cure" compared to 10% of zinc oxide/white petrolatum-treated subjects. The applicant's product was also superior to zinc oxide/white petrolatum for the secondary endpoints "Clinical Cure" (38% vs 11%, respectively) and mycological cure at Day 14 (52% vs 29%, respectively). All of results were statistically significant. Efficacy was not demonstrated in subjects younger than 4 weeks.

The rate of dropouts from the zinc oxide/white petrolatum group was substantially higher than from the group who received treatment with the applicant's product, and the numbers were driven by subjects who were discontinued for being "clinical failures" primarily at the end-of-treatment time point.

In the supportive studies, when clinical clearing was considered for subjects who cultured positive for *Candida albicans* at baseline, the applicant's product trended towards superiority over zinc oxide/white petrolatum in one study and was superior to zinc oxide/white petrolatum in the other study. Assessment was at Day 7 in the supportive studies.

### 1.3.3 Safety

A total of 835 infants and young children were enrolled in the four Phase 3 studies, 418 of whom received treatment with the applicant's product, and 417 subjects received zinc oxide/white petrolatum. The duration of treatment was seven days in all of the studies, and application of study drug was at each diaper change. Only study BT100 included a post-treatment assessment (Day 14).

Adverse events were reported for 143 of the 835 subjects (17%) participating in the four Phase 3 studies: 58 of 418 subjects (14%) received treatment with the applicant's product, and 85 of 417 subjects (20%) received treatment with zinc oxide/white petrolatum. The most common adverse events were infections and infestations (8% for the applicant's product, 12% for zinc oxide/white petrolatum), gastrointestinal disorders (2% for the applicant's product, 3% for zinc oxide/white petrolatum), and respiratory, thoracic and mediastinal disorders (3% for the applicant's product, 2% for zinc oxide/white petrolatum). One of 418 (0.2%) subjects treated with the applicant's product and two of 417 (0.5%) subjects treated with zinc oxide/white petrolatum experienced adverse events that may have been related to study treatment. There was no consistent difference in the occurrence of types of adverse events when the miconazole nitrate and zinc oxide/white petrolatum groups were compared.

### 1.3.4 Dosing Regimen and Administration

The product is to be applied to the diaper area at every diaper change, and the treatment duration is seven days. Dose-finding studies were not conducted.

### 1.3.5 Drug-Drug Interactions

The applicant did not conduct drug-drug interaction studies. On February 28, 2001, the Center for Drug Evaluation and Research issued a Science Background statement regarding the safety of miconazole vaginal cream and suppositories. Specifically, the statement advised health care professionals that, "women who take a warfarin anticoagulant and use a miconazole intravaginal

## 2 INTRODUCTION AND BACKGROUND

### 2.1 Product Information

The applicant's product contains three active ingredients: miconazole nitrate, zinc oxide and white petrolatum. The applicant's proposed indication is treatment of diaper dermatitis complicated by candidiasis.

Miconazole is an azole antifungal of the imidazole class. Other imidazole antifungals include ketoconazole, clotrimazole, econazole, and oxiconazole. Azoles are thought to inhibit fungal growth through impairment of biosynthesis of ergosterol, the primary sterol for the cytoplasmic membrane.<sup>1,2,3</sup> Azoles inhibit a cytochrome p-450-dependent enzyme, lanosterol 14 $\alpha$ -demethylase, resulting in the prevention conversion of lanosterol into ergosterol. Ultimately, growth of fungal cells and permeability of fungal cell membranes are compromised.<sup>2,3</sup> Administration routes for imidazole antifungals include systemic (oral, intravenous), topical, and intravaginal. Marketed formulations of miconazole include cream, spray, powder, and lotion.<sup>1</sup> Topical azoles are reported as generally well-tolerated; however, irritation and burning are among the effects that have been reported.<sup>2</sup>

### 2.2 Currently Available Treatment for Indications

There are several products marketed over-the-counter for diaper rash; however, there is no prescription product marketed in the United States (U.S.) for this indication.

Diaper dermatitis is an umbrella diagnosis that speaks more to the location of an eruption than its etiology. The diagnosis may reflect an eruption that is coincidentally in the diaper area (e.g. seborrheic dermatitis) or an inflammatory process that is a function of conditions in the diaper environment. It is likely the latter category into which the diagnosis of "diaper dermatitis" most often falls, and it is a subset of this category that the applicant proposes to treat. In this review, "diaper dermatitis" refers to this latter category.

Skin wetness is a critical element in the pathogenesis of diaper dermatitis in at least two important ways: wet skin has an increased coefficient of friction and wet skin is more permeable, allowing for more ready penetration of irritants.<sup>4</sup> Friction and irritation play critical roles.<sup>5,6,7</sup> Causative and/or contributory factors may include moisture, urine pH, feces, proteolytic enzymes, soaps and detergents.<sup>5,6,7,8</sup> Infection by *Candida albicans* may secondarily complicate the underlying process.<sup>8,9</sup> *Candida* may exacerbate the inflammation by the release of keratinases.<sup>9</sup> However, there is information suggesting that *Candida albicans* may play a primary role in causing some diaper dermatitis.<sup>7</sup>

At its core, treatment of diaper dermatitis requires strict attention to maintaining a clean, dry diaper environment. Gentle cleansing and frequent diaper changes are fundamental to this. Skin protectants, such as the zinc oxide and white petrolatum in the applicant's product, may be soothing and provide a barrier between the skin and the diaper contents. Some cases of diaper dermatitis may resolve with these measures alone. If the situation is complicated by candidiasis, an antifungal would be added to regimen.

### 2.3 Availability of Proposed Active Ingredient in the United States

Miconazole nitrate is marketed in the U.S. in a variety of formulations. Indications include vulvovaginal candidiasis, tinea cruris, and tinea pedis. Marketed concentrations are 2% and 4% and dosing regimens vary.

On February 28, 2001, the Center for Drug Evaluation and Research issued a Science Background statement regarding the safety of miconazole vaginal cream and suppositories. Specifically, the statement advised health care professionals that, "women who take a warfarin anticoagulant and use a miconazole intravaginal cream or suppository may be at risk for developing an increased prothrombin time, international normalized ratio (INR) and bleeding."<sup>10</sup> The risk of this interaction with warfarin had been known following systemically administered miconazole. Labeling changes were recommended to advise consumers of this risk from use of the vaginal products.<sup>10,11</sup>

### 2.4 Important Issues With Pharmacologically Related Products

There are two classes of azole antifungal agents: the imidazoles and the triazoles. Most azoles under current development are reportedly of the triazole class primarily because:

- Systemic triazoles are metabolized more slowly.
- Systemic triazoles are said to have less effect on sterol synthesis in humans as compared to the imidazoles.<sup>1</sup>

The most common adverse reaction reported for azoles is gastrointestinal upset. Nausea and vomiting have been reported with systemically administered azoles. All azoles have reportedly been shown to cause liver enzyme abnormalities, and the potential for hepatotoxicity may be a significant concern.<sup>12,13</sup>

Candidal resistance may emerge during prolonged treatment with azoles and is primarily limited to the immunosuppressed population. With *Candida albicans*, the primary mechanism for development of resistance is said to be accumulations of the gene that codes for the C14- $\alpha$ -sterol demethylase. Importantly, cross resistance is extended to all other azoles.<sup>1,14</sup>

### 2.5 Presubmission Regulatory Activity

IND 21,542 is associated with NDA 21-026.  
Johnson & Johnson Baby Products Company submitted NDA on June 20, 1985, and  
Per the Medical Officer's review,  
NDA contained data from two single-investigator Phase 3 studies, conducted under the  
same protocol (10833/10842.33) at different study centers. **b(4)**

*Comment: At some point, study 10833/10842.33 came to be referred to as one study with two investigators, rather than two single-investigator studies. It is referred to as one study with two investigators in the Medical Officer's review of the original submission of NDA 21-026 and throughout the applicant's resubmission. Therefore, 10833/10842.33 will be considered as one study in review of the resubmission.*

While the indication did not appear to be expressly stated in the Medical Officer's review of NDA [redacted] the protocol was entitled, "An Evaluation of the Efficacy of BPC Formula No. 610-58 in Treatment of Acute Infantile Diaper Dermatitis and Prevention of Onset of Severe Diaper Dermatitis."

A not-approvable letter was issued for NDA [redacted] on April 22, 1986.

b(4)

b(4)

Following discussions with the Agency, the applicant, now Johnson & Johnson Consumer Products Companies, Inc., conducted two additional Phase 3 studies, and on August 24, 1998, NDA 21-026 was submitted. The submission included the data from three clinical trials: two new Phase 3 trials (12966.37A and 12966.37B; both conducted in Australia) and a pharmacokinetic study (12966.37C; conducted in Mexico). The proposed indication was "treatment of moderate to severe diaper dermatitis where *Candida albicans* may be a contributing factor,"

On June 28, 1999, a not-approvable action was taken on NDA 21-026, with the following clinical deficiencies cited:

1. The indication requires clear-cut definition so that the product may be recommended for a 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.
2. Any planned clinical trial should have sufficient representation from both sexes and from minorities to permit proper subset analysis.
3. The possibility of adverse effect by the ointment base should be addressed in a 3-arm study which includes a treatment group not exposed to the ointment base.
4. The relevance of the dermal safety studies should be addressed, especially with respect to (i) target population being infants and not adults, (ii) test sites not in diaper area, and (iii) appropriateness of using UVA alone in phototoxicity testing and in the challenge phase of the photoallergenicity study.

A complete response to the not-approvable letter was received on January 24, 2000. The submission contained no new data, but included the applicant's responses to the deficiencies outlined in the not-approvable letter. The complete response submitted January 24, 2000 was also determined to be not approvable (letter date July 24, 2000). The clinical deficiencies cited in that letter were that the applicant needed to conduct,

"an adequate and well controlled clinical trial in which the severity of disease is adequately defined and *Candida albicans* involvement adequately documented, that demonstrates the safety and efficacy of miconazole nitrate

ointment and the contribution of each of its active components (21 CFR 300.50), in those clinical subsets that correspond to your proposed indication. Any planned clinical trial should have sufficient representation from both genders and from minorities. Prolonged treatment beyond 7 days, repeated usage for relapse, and development of antifungal resistance should be addressed.”

On June 30, 2000, the application was discussed at a meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee. The questions posed to the committee pertained to the appropriateness of “diaper dermatitis” for the applicant’s antifungal-containing product and whether additional safety and efficacy information were needed. The committee voted against “diaper dermatitis” as an indication for a product that contained an antifungal and that additional safety and efficacy information were needed.

Over the years following the not-approvable letter issued July 24, 2000, the applicant has had numerous meetings with the Agency on how they might proceed in their development program. Considerable discussion was devoted to how the applicant planned to address the combination policy (21 CFR 300.50) in their development program. The applicant considered that miconazole nitrate was the only active ingredient, while the Agency considered the product to be a combination with three active ingredients: miconazole nitrate, zinc oxide and white petrolatum, since zinc oxide and white petrolatum are considered active ingredients in the over-the-counter environment.

Barrier Therapeutics, Inc. acquired responsibility for NDA 21-026 on June 21, 2002 (Section 8.2 of the resubmission). In a teleconference held on December 18, 2003, the applicant was advised that,

“(T)he sponsor’s drug must meet the combination policy because the Agency believes that the zinc oxide and petrolatum are active. The Sponsor does not need to do a specific study to demonstrate the contribution of zinc oxide and petrolatum, however, and can rely on evidence already known regarding the contribution of zinc oxide and petrolatum to the combination. The study should show the contribution of the miconazole.”

It is noted that the not-approvable letters issued on June 28, 1999 and July 24, 2000 advised that the applicant conduct one trial.

## 2.6 Other Relevant Background Information

According to the applicant, topical 0.25% miconazole nitrate ointment has been commercially available outside of the U.S. since 1993. The initial approval was obtained by Johnson & Johnson (Jansen Pharmaceutica) in Belgium in 1991. Johnson & Johnson (Jansen Pharmaceutica) submitted marketing authorization filings (including in the U.S.),

b(4)

The applicant describes that in 2002, they acquired the rights to market a topical 0.25% miconazole nitrate ointment in countries where Johnson & Johnson was not marketing the product. In 2003, Barrier Therapeutics NV, a subsidiary of Barrier Therapeutics, submitted a marketing authorization to the Belgian authorities for Zimycan™, a 0.25% miconazole nitrate “cutaneous paste.” The marketing authorization was granted in May 2004.

According to the applicant, a topical 0.25% miconazole nitrate ointment is marketed over-the-counter for diaper dermatitis in eight countries.

b(4)

*Comment: There is a population for whom safety and efficacy of the applicant's product have not been evaluated: incontinent adults with perineal dermatitis complicated by candidiasis. Hospital distribution may result in use of the product in this adult population.*

### 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

#### 3.1 CMC (and Product Microbiology, if Applicable)

The applicant's product has three active ingredients: miconazole nitrate, zinc oxide and white petrolatum. Per Section 2.3 of the submission, zinc oxide and white petrolatum also serve as part of the delivery vehicle. The composition of the product, 610-73, is:

Ingredient	Function	% w/w
Miconazole nitrate	Drug substance	0.25
Zinc oxide	Drug substance	15.00
White petrolatum	Drug substance	81.35
Trihydroxystearin	Rheological additive*	
Chemoderm 1001/B	Fragrance	
<b>Total</b>		<b>100.00</b>

b(4)

The formulation used during initial development was, 610-58. This formulation included the fragrance Chemoderm 1001 . Formulation 610-58 was used in study 10833/10842.33 and the topical safety studies. Chemoderm 1001/B is the fragrance in the current formulation, 610-73, . Per Section 2.3.P.4, Chemoderm 1001/B is also referred to as Fragrance.

b(4)

Per the chemistry reviewer, the applicant did not list the manufacturing site(s) for the active ingredients zinc oxide and white petrolatum in the FDA 356h Form of the resubmission. The resubmission did not contain the information required to permit assurance of the identity, strength, quality, and purity of the drug substances zinc oxide and white petrolatum.

Miconazole shows absorption peaks at approximately  
Zinc oxide absorbs over most of the UV-A and UV-B spectrum.

#### 3.2 Animal Pharmacology/Toxicology

The pharmacology/toxicology reviewer considered the submission of April 24, 1998 to be approvable with labeling changes, and from the pharmacology/toxicology perspective, the resubmission is being reviewed for labeling only. According to the pharmacology/toxicology

review (completion date April 28, 1999), miconazole nitrate was a "mild to moderate skin irritant and was not an ocular irritant..." A six-month dermal toxicity study was conducted in rabbits and local effects were limited to the treatment site. "The NOEL for that study was 40mg/kg/day (HED = 13mg/kg/day, or three times the maximum clinical daily dose." Oral and intravenous animal studies have shown the liver to be the target organ of toxicity. Reproductive and developmental toxicology testing revealed no apparent effects of miconazole on fertility or teratogenicity. Carcinogenicity studies were not submitted. The summary conclusions did not appear to change in the review with completion date April 14, 2000.

#### **4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY**

##### **4.1 Sources of Clinical Data**

The data reviewed were from the applicant's development program.

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**4.2 Tables of Clinical Studies**  
**Modified Applicant ISS\* Table I. All Clinical Studies (Clinical Pharmacology/Phase III) Supporting Safety of 0.25% Miconazole Nitrate Ointment**

Study No. Investigator(s)	Study Title (Study Dates)	Study Design	Treatment	# Subjects (#/Treatment)	Mean Age (Age Range)
83-513T Warsaw	Phototoxicity Test (10/25/83-10/28/83)	open-label	Patch applied to each forearm for 24 hours. One forearm irradiated with UV-A light. <sup>a</sup>	10 (2/8)	N/A (23-60 years)
83-513A Warsaw	Photoallergy Test (10/31/83-12/8/83)	Open-label	Patch applied to each forearm for 24 hours 2x/week for 3 weeks. One forearm irradiated with UV-A & UV-B light after each application. After 10-14 day rest period, challenge patch applied to virgin site of each forearm & one forearm irradiated with UV-A light. <sup>a</sup>	31 (2/29)	N/A (20-63 years)
83-129 Warsaw	Repeated Insult Test/Draize Sensitization Test (12/5/83-1/13/84)	open-label	Patch applied to upper back for 24 hours 3x/week for 3 weeks. After 10-14 day rest period, 2 consecutive challenge patches applied to virgin site of back. <sup>a</sup>	216 (60/156)	N/A (18-68 years)
227.0184 Kantor	Cumulative Irritation Test (1/25/84-2/8/84)	open-label	Patches with active & control product applied to upper back for 48 or 72 hours 3x/week for 2 weeks. <sup>b</sup>	26 (1/25)	N/A (18-65 years)
12966.37C Herrera	Study of Absorption & Efficacy of Miconazole Nitrate in Infants with Diaper Dermatitis Associated with Systemic Pathology (7/19/88-6/14/89)	open-label, uncontrolled, noncrossover	0.25% or 2% miconazole nitrate applied to clinically affected area at each diaper change for 7 days. Blood samples collected before and at the end of treatment. <sup>c</sup>	24 [19, 0.25%; 5, 2%] (12/12)	6.87 months (1-12 months)
10833/10842.33 Manners and Silverman (402)	A Multicenter Evaluation of BPC Formula No. 610-58 in Treatment of Acute Diaper Dermatitis in Infants (11/7/83-6/23/84)	Phase 3, randomized, DB, PCB, parallel	0.25% miconazole nitrate (MN) or vehicle control (VC) applied to clinically affected area at each diaper change for 7 days.	107 [53 MN 54 VC] (48/59)	7.1 months (1.8-12.0)
12966.37A Concannon (403A)	An Evaluation of the Efficacy of BPC Formula No. 610-73 in Treatment of Acute Diaper Dermatitis in Infants (2/27/89-3/21/90)	Phase III, Randomized, DB, PCB, parallel	0.25% miconazole nitrate (MN) or vehicle control (VC) applied to clinically affected area at each diaper change for 7 days.	202 [101 MN 101 VC]	5.7 months (1.7-13.0)
12966.37B Wagner and Lillystone (403B)	A Multicenter Evaluation of the Efficacy of BPC Formula No. 610-73 in Treatment of Acute Diaper Dermatitis in Infants (12/7/88-11/10/89)	Phase III, Randomized, DB, PCB, parallel	0.25% miconazole nitrate (MN) or vehicle control (VC) applied to clinically affected area at each diaper change for 7 days.	196 [98 MN 98 VC] (91/105)	5.8 months (1.7-12.3)
BT100 USA/001 Multiple	A Double-Blind, Randomized, Multi-Center Study of 0.25% Miconazole-Nitrate Ointment in the Treatment of Cutaneous Candidiasis Complicating Diaper Dermatitis(4/3/03-6/30/04)	Phase III, Randomized, DB, multi-center	0.25% miconazole nitrate (MN) or vehicle control (VC) applied to clinically affected area at each diaper change for 7 days.	330 [166 MN 164 VC] (145/185)	9.16 MN 9.97 VC (0.4-35.2) Months

\*Integrated Summary of Safety  
a 0.2 to 0.3 ml of 0.25% miconazole nitrate ointment (BPC 610-58) applied to an occlusive patch MN = 0.25% miconazole nitrate ointment PCB = Placebo-controlled  
b 0.2 to 0.3 ml of 0.25% miconazole nitrate ointment (BPC 610-58) or vehicle control applied to an occlusive patch VC = vehicle control  
c 0.25% miconazole nitrate ointment (Janssen F100) or 2% miconazole nitrate cream DB = Double-blind  
MN = 0.25% miconazole nitrate ointment  
VC = vehicle control  
DB = Double-blind PCB = Placebo-controlle

#### 4.3 Review Strategy

The primary focus of this review is the data from the new Phase 3 trial, BT100 USA/100 (BT 100). The other Phase 3 trials were the subject of thorough review when NDA 21-026 was originally submitted. The Medical Officers reviews of NDA 21-026 were reviewed. The previously-submitted data were not "re-reviewed" in their entirety. Review of those data was limited to what was included in applicant's resubmission and what was presented in the Medical Officers reviews.

b(4)

For purposes of this review, the applicant's product is referred to as "0.25% miconazole nitrate" ointment and the zinc oxide/white petrolatum comparator is referred to as "vehicle." This approach is only for review purposes. From a regulatory perspective, miconazole nitrate, zinc oxide and white petrolatum are all considered active ingredients.

#### 4.4 Data Quality and Integrity

Division of Scientific and Investigations (DSI) audit was requested of sites 9 and 19. The rationale for requesting inspection of site 9 was that this site had a delta between success and failure that was wider than the overall cure rate for the study. The rationale for requesting inspection of site 19 was that this site had a 33% overall cure rate for 0.25% miconazole nitrate vs. 0% for vehicle. Additionally, site 19 had a 67% clinical cure rate for 0.25% miconazole nitrate vs. 0% for vehicle. The overall cure rates were 23% for 0.25% miconazole nitrate and 10% for vehicle and a 38% clinical cure rate for 0.25% miconazole nitrate and 11% for vehicle.

Although both inspections had been completed, the final reports were not available as this review was being drafted. However, the review division was provided preliminary information indicating that no "problems" or "serious issues" were raised from the inspections of either site (April 7<sup>th</sup> electronic communication).

#### 4.5 Compliance with Good Clinical Practices

As noted in Section 4.4, Site 19 drew attention because of the reported cure rates. This site enrolled 41 subjects. Review of Listing 16.2.6.1, "Clinical Evaluations-Observed," revealed that all 41 subjects enrolled at this site had erosions baseline. The reviewer considers this an unusual set of circumstances for presentation of this number of subjects, i.e. that all 41 subjects presented with erosions. This pattern was not reported for any other study site. Erosions for 28 of 41 subjects (68%) were resolved at Day 7, the end-of-treatment visit, a seemingly high rate of resolution for this time point. Additionally, 19 of 41 subjects (46%) had identical baseline scores for each of the signs assessed (and thus for diaper dermatitis severity score). Those scores were erythema: 2, papules/pustules: 2, and erosions: 1 (although the presence of erosions automatically conferred a score of 1 for this sign, as they were graded as either "present" or "absent.")

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#### 4.6 Financial Disclosures

The applicant appears to have adequately disclosed financial arrangements with clinical investigators by certifying that they had not entered into any financial arrangement with any of the clinical investigators.

### 5 CLINICAL PHARMACOLOGY

#### 5.1 Pharmacokinetics

The applicant conducted an open-label, uncontrolled clinical pharmacology study (12966.37C) in 24 infants ages 1-12 months who were hospitalized for treatment of gastroenteritis and who had moderate to severe diaper dermatitis. The extent of absorption following topical application of miconazole nitrate 0.25% ointment or miconazole nitrate 2% cream was assessed. Study products were applied after each diaper change, and the study duration was seven days (although the discussion of the study in Section 8.8.1.0 of Volume 17 does not appear to expressly state that the study products were applied for seven days.)

Blood samples were obtained before treatment on Day 1 and on Day 7. The applicant reports that plasma concentrations were below the lower limit of detection (<1.0 ng/mL) for 15 of 18 infants (83%) treated with miconazole nitrate 0.25% ointment and < 5 ng/mL for the remaining 3 infants (17%). Samples from one infant were reported to have been missing. Blood concentrations ranged from 5.2 to 7.4 ng/mL in four of the five infants (80%) treated with 2% miconazole nitrate cream. Miconazole was below the lower limit of detection in one infant.

*Comment: In the review dated April 21, 1999, the clinical pharmacology/biopharmaceutics reviewer concluded that, "The applicant has demonstrated very low exposure of miconazole from the product on topical application. Adequate information from the literature has been provided on the metabolism, distribution and elimination of miconazole from oral and intravenous forms of the product." The clinical pharmacology/biopharmaceutics reviewer recommended approval of the submission of April 24, 1998 (review date April 21, 1999), and the resubmission under current review is being reviewed for labeling only.*

At the request of the clinical pharmacology/biopharmaceutics reviewer, the applicant conducted an *in vitro* study to investigate the release of elemental zinc (Zn) from their product. Per the clinical pharmacology/biopharmaceutics review, the study was conducted using occluded Franz Cell model and human cadaver skin and included placebo and tissue controls to quantitate the extent of Zn in the receptor medium from release of endogenous tissue Zn. The clinical pharmacology/biopharmaceutics reviewer concluded that, although there were "not very critical" deficiencies in the study design, there were "very low amounts of zinc release in the receptor solution."

The applicant's development program did not include drug interaction or disease interaction studies. However, there have been reports of prolonged international normalized ratios (INR) in subjects taking warfarin who subsequently began using miconazole. Reports of this interaction include its occurrence with intravaginal administration of miconazole.<sup>15</sup> Miconazole and

warfarin are both metabolized by cytochrome P450 2C9. There are reportedly known interactions with amphotericin B and phenytoin. There may also be a potential for miconazole to interact with rifmapin and cyclosporine because of its structural similarity to ketoconazole.<sup>15</sup>

Applicant Table 7. Summary of Pharmacokinetic Studies

Reference Number	Study Type	Subjects	Route of Administration	Dose (mg)	Dose Regimen	Peak Miconazole Concentration (ng/mL)	Tmax (hr)	Cumulative Excretion	
								Urine	
PK-5	A	Pediatric	Topical (0.25%) Topical (2%)	10 <sup>b</sup>	7 Days	<1.0 – 3.8 <sup>c</sup> 5.2 – 7.4 <sup>c</sup>	-	-	-
PK-6, PK-7	M,E E E	Adult Adult Adult	Oral Oral Topical (2%)	50 <sup>d</sup> 1000 <sup>e</sup> 20	Single Dose Day 2 and 15 <sup>e</sup> Single Dose	290 – 390 <sup>c,f</sup> 1.8 - 2.2 103 <sup>c,f</sup> 2.6 <sup>c,f</sup>	4 4 -	17.8 13.0 0.35	43.8 49.6 -
PK-11	A	Adult	Topical (2%)	100	Single Dose	<10 <sup>g</sup>	ND	-	-
PK-12	A	Adult	Intravaginal	100	7 Days	8.84 <sup>f,h,i</sup>	10-12	1.03%	0.85%
PK-13	A	Adult	Intravaginal	100 200	7 Days 3 Days	12.68 <sup>h,i</sup> 8.840 <sup>h,i</sup>	12	-	-
PK-14	A	Adult	Intravaginal	1200	Single Dose	10.4 <sup>f</sup>	6-24	-	-
PK-15	A,D	Adult	Intravenous	522	Single Dose	2020-9100	0.25	-	-
PK-16	A,D,E	Adult	Oral Tablet Oral Gel	500 500	Single Dose Single Dose Single Dose	1240 1790	2-4	-	-
PK-17	CR	Pediatric	Intravenous	5	Single Dose	1600	-	-	-
PK-18	CR	Pediatric	Intravenous Intravenous Intravenous Intravenous	3.8 <sup>j</sup>  6.9 <sup>j</sup> 6.0 <sup>j</sup> 4.0 <sup>j</sup>	Multiple doses Multiple doses Multiple doses Multiple doses	530 1260 650 710	2.0 2.0 2.0 1.0	-	-
PK-19	CR	Pediatric	Intravenous	4.0 <sup>j</sup> 7.4 <sup>j</sup>	6 Days 7 Days	400 400	0.5 0.5	-	-
PK-20	CR	Pediatric	Intravenous	8.9 <sup>j</sup> 10.5 <sup>j</sup>	Multiple doses Multiple doses	1600 3600	1.0 1.0	-	-

A=Absorption D=Distribution M=Metabolism E=Excretion CR = Case report from published literature  
 a Mean percent of administered radioactivity recovered (see text for time period) Days 1, 3-14, 16-28: 1000 mg unlabelled miconazole t.i.d.  
 b Estimated dose based on regimens used in pivotal clinical trials (90th percentile) f ng equiv/mL (total plasma radioactivity)  
 c Range (limit of detection < 1 ng/mL) g Limit of detection 10 ng/mL  
 d 50 mg 3H miconazole single dose (with 6 day washout) h After last dose  
 e Days 2 and 15: Single dose of 250 mg 3H-miconazole + 750 mg unlabelled miconazole q.d. i Mean value  
 + 1000 mg unlabelled miconazole b.i.d. j Mg/kg

The pharmacology/toxicology reviewer concluded that absorption, distribution, metabolism and excretion studies revealed low absorption of miconazole after dermal application (review completion date: April 28, 1999). After topical application, distribution was primarily to the liver, kidney, lung, adrenal glands and thyroid. The pharmacology/toxicology review describes miconazole as being highly metabolized in man and animals and excreted primarily in the bile, with enterohepatic recirculation.

## 5.2 Pharmacodynamics

The applicant did not conduct pharmacodynamic studies.

### 5.3 Exposure-Response Relationships

The applicant did not conduct dose-response studies.

## 6 INTEGRATED REVIEW OF EFFICACY

### 6.1 Indication

The indication has been the subject of much discussion in the development of this product. Zinc oxide and white petrolatum are skin protectants found in products currently marketed for diaper rash. However, the antifungal in the applicant's product necessitates an indication that requires antifungal treatment. Diaper dermatitis does not always have the complication of candidiasis, and in the absence of such, there would be no justification for treating the eruption with an antifungal-containing product. The indication proposed in the resubmission is "treatment of diaper dermatitis complicated by candidiasis." This is a more appropriate proposed indication for the applicant's product.

While the proposed indication did not appear to be expressly stated in the Medical Officer's review of NDA \_\_\_\_\_, the titles of the study conducted in support of that application were, "An Evaluation of the Efficacy of BPC Formula No. 610-58 in Treatment of Acute Infantile Diaper Dermatitis and Prevention of Onset of Severe Diaper Dermatitis." Fungal cultures were obtained pre-treatment and at the end of treatment; however, there were no microbiological criteria for determination of study eligibility.

The proposed indication in the original submission of NDA 21-026 was "treatment of moderate to severe diaper dermatitis where *Candida albicans* may be a contributing factor." As was the case for the study conducted in support of NDA \_\_\_\_\_, there were no microbiological criteria for determination of study eligibility.

#### 6.1.1 Methods

This efficacy review focuses on the clinical data from the new Phase 3 trial, BT 100 USA/001 (BT 100). The previously-conducted Phase 3 trials were thoroughly reviewed in the original submission of the NDA 21-026 and will be presented in summary form in this review (see Section 6.1.4).

#### 6.1.2 General Discussion of Endpoints

The proposed indication for the applicant's product has a clinical element (diaper dermatitis) and a microbiological element (candidiasis). While there may be some overlap in the clinical presentation of diaper dermatitis and cutaneous candidiasis (e.g. erythema), clinical clearing would not necessarily indicate mycological eradication, and without mycological eradication there would be no acceptable justification for the antifungal in the product. Similarly,

demonstration of mycological eradication would mean little in the absence of clinical benefit, i.e. clearing of the dermatitis. Therefore, for demonstration of efficacy,

- The applicant's product should demonstrate that it is effective in clearing the clinical signs of diaper dermatitis.
- The applicant's product should demonstrate that it is effective in eradicating *Candida albicans*.

The primary endpoint in the new study, BT 100, was "Overall Cure" which required that subjects be assessed as both clinically cured (i.e. Diaper Dermatitis Severity Index Score of 0) and microbiologically eradicated. The Diaper Dermatitis Severity Index Score was a global assessment that reflected erythema, papules or pustules, and erosions and is further discussed in Section 6.1.3.

*Candida albicans* are part of the normal skin flora.<sup>16,17,19,20</sup> Therefore, its demonstration on culture would not have been sufficient evidence of infection, and other information was needed to indicate invasion. For this reason, the applicant was advised that in addition to fungal cultures, microscopic evaluations needed to be done to demonstrate the presence of pseudohyphae (and/or budding yeast). Thus, fungal cultures and KOH were required for diagnosis of candidal infection at baseline.

### 6.1.3 Study Design

Reasonable and adequate efforts appear to have been made to minimize bias, in that study BT100 was randomized, double-blind, multi-centered, and vehicle-controlled. Additionally, the statistical analysis plan was put forward prospectively. The choice of zinc oxide/white petrolatum as the control group was acceptable and in line with the agreement that the applicant's study be designed to demonstrate the contribution of miconazole to efficacy.

In study BT100, subjects were required to have positive KOH (pseudohyphae and/or budding yeast) and culture for *Candida spp.* and a Diaper Dermatitis Severity Index Score of 3-8 at baseline. The Diaper Dermatitis Severity Index Score was a global assessment that reflected three clinical signs:

Score	Erythema	Papules or Pustules	Erosions
0	None to trace	None to trace	absent
1	Mild (pink)	Few (1-10)	present
2	Moderate (red)	Multiple (11-20)	NA
3	Severe (beefy red)	Many (21-40)	NA
4	NA	Abundant (>40)	NA

NA= not applicable

A Diaper Dermatitis Severity Index Score of 3-8 was required for study eligibility with at least a score of 2 for erythema.

*Comment: The requirement to document candidal infection by microscopic examination should apply to the clinical arena, i.e. under real-use conditions, and be reflected in labeling.*

The Inclusion and Exclusion Criteria follow:

**Inclusion Criteria:**

1. Male and female neonates, infants, and children 2 through 4 years of age with Fitzpatrick Skin Type I-VI, who wear commercially available diapers day and night.
2. Subjects with clinical evidence of diaper dermatitis and a positive KOH sample for pseudohyphae and/or budding yeast at baseline visit.
3. Subjects must have an overall diaper dermatitis severity index score of 3-8 at baseline visit (Study Day 0) in order to be enrolled into the study. This score must include an overall clinical grade of at least 2 for erythema.
4. Subjects wearing commercially available diapers (day and night) for at least 7 days prior to enrollment on Study Day 0 and during the course of the study.
5. Care taker (parents or legal guardian) has signed the Informed Consent Form.

**Exclusion Criteria:**

1. Known sensitivity to any of the formulation components.
  2. Any skin conditions present (i.e. atopic dermatitis, seborrheic dermatitis, psoriasis, and acrodermatitis enteropathica) other than diaper dermatitis that may require concurrent therapy or may confound the evaluation of drug efficacy and tolerability.
  3. Known sensitivity to skin care toiletry products or diapers.
  4. Chronic illnesses requiring systemic medication that may confound the evaluation of drug efficacy and tolerability (i.e. antihistamines, corticosteroids, and insulin).
- Note: Chronic antibiotic therapy will not exclude a child from this study.
5. Subjects who have been treated with a prescription product (e.g., corticosteroids) for diaper dermatitis or any other skin condition 7 days prior to enrollment.
  6. Subjects who have previously been randomized into this protocol.

*Comment: The Inclusion and Exclusion criteria were appropriate for this study.*

Subjects were randomized to treatment with either 0.25% miconazole nitrate or vehicle at the baseline visit. Subjects were evaluated at Day 0 (baseline), Day 3, Day 7 (end-of-treatment), and Day 14 (test-of-cure). The protocol also allowed for an optional visit at Day 5. If an enrolled subject's baseline culture was negative, that subject was discontinued at Day 3 or at subsequent visits. Clinical evaluations were conducted at each of these visits. A follow-up telephone contact was made on Day 28 to inquire about recurrence.

The primary endpoint in BT 100 was "Overall Cure" which required that subjects be assessed as both clinically cured and microbiologically eradicated one at Day 14 (one week post-treatment), the test-of-cure visit.

Dose-finding studies were not done. There are no products marketed at the 0.25% concentration in the U.S. In Section 8.7.1 of the Integrated Summary of Efficacy, the applicant states that,

"This 0.25% miconazole nitrate ointment was developed specifically for infants for the treatment of the semi-occluded diaper area, with a reduced concentration of miconazole nitrate."

However, by agreement with the Agency, only miconazole nitrate's contribution to efficacy was required to be demonstrated in the study submitted in support of this resubmission. Specifically, the applicant was advised that they could, "rely on evidence already known regarding the contribution of zinc oxide and petrolatum to the combination" (December 18, 2003 teleconference).

As background to the discussion of efficacy in the Integrated Summary of Efficacy, the applicant included a general discussion of diaper dermatitis, including mention of zinc oxide and petrolatum. Additionally, literature references were included in the submission. However, the applicant did not designate any portion of the submission as specifically being the "evidence already known regarding the contribution of zinc oxide and petrolatum" on which they would rely.

While the contribution of the zinc oxide and white petrolatum to efficacy were not evaluated, implicit in the applicant's proposed indication, "treatment of diaper dermatitis complicated by candidiasis" is some acknowledgment of their contribution to efficacy: diaper dermatitis is the underlying process and miconazole nitrate is not a recognized treatment for "diaper dermatitis" *per se*. It is noted that review of the observed clinical evaluations (Volume 12, Listing 16.2.6.1) revealed that some subjects in the zinc oxide/white petrolatum group did improve and even clear on that treatment.

#### 6.1.4 Efficacy Findings

This efficacy review focuses on the clinical data from the new Phase 3 trial, BT 100. The previously-conducted Phase 3 trials were thoroughly reviewed in the original submission of NDA 21-026 and will be presented in summary form following review of data from BT 100.

#### Disposition of Subjects

A total of 330 subjects were enrolled in BT 100, 236 of whom were included in the modified intent-to-treat (MITT) population. Per the protocol, the MITT population was defined as "all subjects with confirmed *Candida spp.* who were dispensed study medication (active or vehicle)."

**Summary of Subject Enrollment and Evaluability BT 100 (modified Applicant Table 10.1.1)**

	<b>0.25% Miconazole Nitrate Ointment</b>	<b>Vehicle</b>	<b>Total</b>
Enrolled	166	164	330
Excluded from MITT	54	40	94
Included in MITT	112	124	236
Excluded from PP	24	19	43
Included in PP	88	105	193

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#### **Summary of Discontinuation Reasons-All Subjects BT 100 (Applicant Table 10.1.2)**

	0.25% Miconazole Nitrate Ointment	Vehicle	Total
Total Number of Subjects Randomized	166	164	330
Completed Test-of-Cure Visit			
Yes	108	66	174
No	58	98	156
Primary Reason for Discontinuation			
Negative Baseline Culture for Candida	45	34	79
Clinical Failure/Worsening/No improvement	4	59	63
Adverse Event	0	1	1
Subject Withdrew Consent	1	2	3
Protocol Violation	1	1	2
Lost to Follow-up	7	1	8

**Summary of Discontinuation Reasons-MITT Population (Sponsor Table 10.1.2)**

	0.25% Miconazole Nitrate Ointment	Vehicle	Total
Number of Subjects in MITT Population	112	124	236
Completed Test-of-Cure Visit			
Yes	99	61	160
No	13	63	76
Primary Reason for Discontinuation			
Clinical Failure/Worsening/No improvement	4	58	62
Adverse Event	0	1	1
Subject Withdrew Consent	1	2	3
Protocol Violation	1	1	2
Lost to Follow-up	7	1	8

*Comment: Per listing 16.2.8. ("Microbiology"), several subjects who had baseline negative cultures had positive baseline KOH preparations. One possible explanation for this discrepancy is that there may have been some problem in the handling of the specimens that impacted their viability for culture (e.g. in transport to lab). Discontinuations will be further discussed later in the review.*

**Data Sets Analyzed**

An MITT analysis was conducted on all subjects who were randomized, received study drug, and had a positive baseline culture and for tests of the "Overall Cure".

**Demographics and Other Baseline Characteristics**

There was a significant difference in ages when the miconazole nitrate group was compared to vehicle. Mean and median ages were higher for the vehicle group. This may be a function of there being more subjects in the < 3 months of age in the miconazole nitrate group and more subjects in the 24 ≤ to < 36 in the vehicle-treated group. However, most subjects in both treatment groups were in the 6 months ≤ to < 12 months age range, and this range captures the age group in which diaper dermatitis most frequently occurs, i.e. between 9 and 12 months of age.<sup>4,9,18</sup> There were no significant differences between treatment groups for gender or race.

**Demographic Characteristics MITT (Sources: Applicant's Tables 14.1.5 and 14.1.8)**

	0.25% Miconazole Nitrate Ointment	Vehicle	p-value
<b>Number of Subjects</b>	112	124	
<b>Age (Months)</b>			
Mean	7.67	9.59	0.019
STD	4.87	6.89	
Median	7.46	7.72	
Range	0.4-24.5	0.6-30.5	
< 3 months	22 (20%)	17 (14%)	
3 ≤ to < 6	21 (19%)	27 (22%)	
6 ≤ to < 12	49 (44%)	46 (37%)	
12 ≤ to < 24	19 (17%)	26 (21%)	
24 ≤ to < 36	1 (1%)	8 (6%)	
36 or older	0 (0%)	0 (0%)	
<b>Gender</b>			
Male	51 (46%)	57 (46%)	0.813
Female	61 (54%)	67 (54%)	
<b>Race</b>			
White	24 (21%)	34 (27%)	0.384
Non-White	88 (79%)	90 (73%)	
Black	14 (13%)	8 (6%)	
Asian/Pacific Islander	0 (0%)	0 (0%)	
Hispanic/Latino	70 (63%)	76 (61%)	
American/Alaskan Native	0 (0%)	1 (1%)	
Other	4 (4%)	5 (4%)	
<b>Fitzpatrick Skin Type*</b>			
I	5 (4%)	7 (6%)	0.748
II	18 (16%)	13 (10%)	
III	18 (16%)	31 (25%)	
IV	49 (44%)	56 (45%)	
V	17 (15%)	11 (9%)	
VI	5 (4%)	6 (5%)	

\*Included in Demographics table for convenience

**Enrollment U.S. sites and Latin Sites (MITT) (Source: Applicant Table 14.1.2)**

	Total N=236	0.25% Miconazole Nitrate Ointment N= 112	Vehicle N=124
<b>U.S. sites</b>	99	45	54
<b>Latin sites</b>	137	67	70

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**Baseline Disease Characteristics**

There were no significant differences in baseline disease characteristics (clinical or mycological).

**Baseline Disease Characteristics (MITT) Source: Applicant's Table 14.1.8**

	<b>0.25% Miconazole Nitrate Ointment n=112</b>	<b>Vehicle N=124</b>	<b>p-value</b>
<b>Erythema</b>			
0 None	0 (0%)	0 (0%)	0.307
1 Mild	0 (0%)	0 (0%)	
2 Moderate	81 (72%)	96 (77%)	
3 Severe	31 (28%)	28 (23%)	
<b>Papules/Pustules</b>			
0 None	0 (0%)	0 (0%)	0.848
1 Few (1-10)	20 (18%)	28 (23%)	
2 Multiple (11-20)	53 (47%)	45 (36%)	
3 Many (21-40)	30 (27%)	40 (32%)	
4 Abundant (>40)	9 (8%)	11 (9%)	
<b>Erosions</b>			
0 Absent	53 (47%)	64 (52%)	0.560
1 Present	59 (53%)	60 (48%)	
<b>Diaper Dermatitis Severity Index Score</b>			
0	0 (0%)	0 (0%)	0.660
1	0 (0%)	0 (0%)	
2	0 (0%)	0 (0%)	
3	9 (8%)	15 (12%)	
4	31(28%)	32 (26%)	
5	38 (34%)	38 (31%)	
6	18 (16%)	22 (18%)	
7	11 (10%)	13 (10%)	
8	5 (4%)	4 (3%)	
Mean	5.05	4.98	0.661
STD	1.25	1.28	
Range	3.0-8.0	3.0-8.0	
<b>KOH</b>			
Positive	112 (100%)	124 (100%)	1.00
Negative	0 (0%)	0 (0%)	
<b>Mycological Culture</b>			
<i>Candida albicans</i>	109 (97%)	121 (98%)	0.788
Other <i>Candida spp.</i>	3 (3%)	3 (2%)	
Both cultures negative	0 (0%)	0 (0%)	
Not reported	0	0	

*Comment: In Section 9.8 of the study report for BT 100, the applicant indicated that they performed an analysis of the Diaper Dermatitis Severity Index Score categorizing subjects as "moderate" (score of 3-4) or "severe" (score of 5-8). This was a post-hoc analysis done "to facilitate the integration" of the BT 100 "with the previous three clinical studies that were submitted." However, the clinical scales used in the other Phase 3 studies were not the same as those used in study BT 100. Further, per the Medical Officer's review of the original submission of NDA 21-026, in one of those Phase 3 studies (10833/10842.33), the use of "moderate" and "severe" categorizations was also introduced on a post-hoc basis. Additionally, for study 12966.37A, the categorizations of "mild", "moderate", and "severe" were not described or*

*defined. Thus, these new categorizations of disease severity in study BT 100 would appear to allow integration with data from the previous Phase 3 studies in name only (at least as pertains to "mild", "moderate", and "severe").*

*It is also noted that no rationale was found for the selection of the cut-offs for these categorizations in study BT 100, and the applicant's classification skews towards the severe category. Given that the severity index was scored on a nine-point scale (0-9), a more appropriate breakdown would seem to have been 0-2-mild, 3-5 moderate and 6-8 severe.*

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**Efficacy Results**

**Applicant's Evaluations at Day 7 End-of-Treatment (MITT) Table 14.2.1.1**

	<b>0.25% Miconazole Nitrate Ointment N= 112</b>	<b>Vehicle N=124</b>
<b>Mycological Culture</b>		
Both cultures negative	43 (38%)	24 (19%)
<i>Candida albicans</i>	57 (51%)	87 (70%)
Other <i>Candida spp.</i>	5 (4%)	2 (2%)
Missing	7 (6%)	11 (9%)
<b>Clinical Response</b>		
Success	27 (24%)	3 (2%)
Failure	85 (76%)	121 (98%)
<b>Microbiologic Response</b>		
Success	43 (38%)	24 (19%)
Failure	69 (62%)	100 (81%)
<b>Therapeutic Response:</b>		
<b>Overall Cure</b>		
Success	8 (7%)	1 (1%)
Failure	104 (93%)	123 (99%)

**Applicant's Evaluations at Day 14 Test-of-Cure (MITT) Table 14.2.1.2**

	<b>0.25% Miconazole Nitrate Ointment N= 112</b>	<b>Vehicle N=124</b>
<b>Mycological Culture</b>		
Both cultures negative	56 (50%)	29 (23%)
<i>Candida albicans</i>	39 (35%)	30 (24%)
Other <i>Candida spp.</i>	3 (3%)	1 (1%)
Missing	14 (13%)	64 (52%)
<b>Clinical Response</b>		
Success	43 (38%)	14 (11%)
Failure	69 (62%)	110 (89%)
<b>Microbiologic Response</b>		
Success	56 (50%)	29 (23%)
Failure	56 (50%)	95 (77%)
<b>Therapeutic Response:</b>		
<b>Overall Cure</b>		
Success	26 (23%)	12 (10%)
Failure	86 (77%)	112 (90%)

*Comment: The progressive improvement in the clinical cure rates in vehicle-treated subjects could reflect that zinc oxide/petrolatum may impact the underlying dermatitis even in the face of candidiasis. The progressive improvement in mycological response rates in vehicle-treated subjects may reflect an indirect contribution of the zinc oxide/petrolatum in that an improved diaper environment would be less favorable to the candida. Given the progressive improvement in the vehicle arm, it is possible that additional subjects may have shown improvement at Day 14 had they remained in the study.*

**Statistical Reviewer's Table A.5: Overall Cure<sup>a</sup> Rate by Visit (MITT) – Study BT100**

Visit	Miconazole (n = 112)	Vehicle (n = 124)	Comparison <sup>b</sup>
Baseline	0	0	--
Day 7	8 (7%)	1 (0.8%)	0.010
Day 14	26 (23%)	12 (10%)	0.005

Source: Sponsor's NDA submission (pages 008 00159-00160) and electronic data at [\cdsesub\21026\000\Hpbio\NDA\\_21-026\BT100-USA-001](#).  
<sup>a</sup>Overall cure is defined as clinical cure (i.e., all sign/symptom scores of 0) plus mycological cure (i.e., negative culture). Missing is based on LOCF.  
<sup>b</sup>p value from CMH test adjusting for investigational group.

**Statistical Reviewer's Table A.6: Clinical Cure<sup>a</sup> Rate by Visit (MITT) – Study BT100**

Visit	Miconazole (n = 112)	Vehicle (n = 124)	Comparison <sup>b</sup>
Baseline	0	0	--
Day 3	0	1 (1%)	--
Day 5	2 (2%)	1 (1%)	--
Day 7	27 (24%)	3 (2%)	< 0.001
Day 14	43 (38%)	14 (11%)	< 0.001

Source: Sponsor's NDA submission (page 008 00189).  
<sup>a</sup>Clinical cure is defined as the resolution of all sign/symptom (i.e., sum of sign/symptom scores of 0). Missing is imputed based on LOCF.  
<sup>b</sup>p value from CMH test adjusting for investigational group.

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Statistical Reviewer's Table A.7: Mycological Response by Visit (MITT) – Study BT100

Visit	Response	Miconazole (n = 112)	Vehicle (n = 124)	Comparison <sup>c</sup>
Baseline	<i>Candida albicans</i>	109 (97%)	121 (98%)	0.788
	Other <i>Candida spp.</i>	3 (3%)	3 (2%)	
	Both cultures negative	0	0	
	Missing	0	0	
Day 7	<i>Candida albicans</i>	57 (51%)	88 (71%)	0.004
	Other <i>Candida spp.</i>	5 (4%)	2 (2%)	
	Both cultures negative	43 (38%)	24 (19%)	
	Missing	7 (6%)	10 <sup>a</sup> (8%)	
	Mycological Cure Rate (LOCF)	43 (38%)	24 (19%)	
Day 14	<i>Candida albicans</i>	39 (35%)	29 (23%)	< 0.001
	Other <i>Candida spp.</i>	3 (3%)	1 (<1%)	
	Both cultures negative	56 (50%)	29 (23%)	
	Missing	14 (13%)	65 <sup>b</sup> (52%)	
	Mycological Cure Rate (LOCF)	58 (52%)	36 (29%)	

Source: Sponsor's NDA submission (pages 008 00152, 00159, and 00160) and electronic data set at \cdsesub\21026\000\Hpbio\NDA\_21-026\BT100-USA-001.  
<sup>a</sup> Based on the sponsor's data sets. Sponsor's submission listed as 11 (9%).  
<sup>b</sup> Based on the sponsor's data sets. The culture on Day 14 for Patient 411 in vehicle arm was not done. Therefore, the culture of Patient 411 should be missing. Sponsor's submission listed as 64 (52%).  
<sup>c</sup> Comparison of distribution of data in various categories. For comparison of mycological cure rate based on the LOCF method for missing data, p value is from CMH test adjusting for investigational group.

*Comment: Per the protocol, "Microbiologic Response" was measured only by culture at the test-of-cure visit. This is acceptable, since the significance of a positive KOH post-treatment would be unclear, e.g. could represent dead microorganisms.*

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**Statistical Reviewer's Table 7: Missing Data Rate over Visit (MITT) – Study BT100**

Visit	Miconazole (n = 112)	Vehicle (n = 124)	Comparison <sup>a</sup>
Baseline	0	0	1.000
Day 7	7 (6%)	10 <sup>b</sup> (8%)	0.591
Day 14	14 (13%)	65 <sup>c</sup> (52%)	< 0.001

**Source:** Sponsor's electronic data at \\cdsesub\21026\000\Hpbio\NDA\_21-026\BT100-USA-001.

<sup>a</sup> p-value from Fisher's exact test.  
<sup>b</sup> Based on the sponsor's data sets. Sponsor's submission listed as 11 (9%).  
<sup>c</sup> Based on the sponsor's data sets. The culture on Day 14 for Patient 411 was not done. Therefore, the culture of Patient 411 should be missing. Sponsor's submission listed as 64 (52%).

*Comment: In the protocol-specified last-observation-carried-forward (LOCF) analysis, miconazole nitrate was superior to vehicle for the primary endpoint of "Overall Cure" at Day 14 (the test-of-cure visit). While the results are statistically significant, less than 25% of miconazole-treated subjects achieved overall cure. Miconazole nitrate was also superior to vehicle for the clinical cure rates and mycological response rates at Day 14, secondary endpoints.*

*While the dropout rates were similar at Day 7, the rates were significantly higher in the vehicle arm at Day 14. Most of the missing data at Day 14 was due to discontinuations. The protocol allowed for a subject's withdrawal based on the clinical judgment of the investigator regarding whether continuing study treatment would be in the best interest of the subject. "Factors that may lead to this determination may be that the dermatological symptoms have 'worsened', that is, the diaper dermatitis severity index score has increased as compared to baseline evaluation, or that insufficient progress has been made regarding resolution of the symptoms." Most of the missing data for vehicle-treated subjects from the Day 14 visit is attributable to discontinuations for "clinical failure." Review of the data listings 16.2.1.1 ("Discontinuations/Completion Information") and 16.2.6.1 ("Clinical Evaluations Observed") suggests most of these subjects were judged to be clinical failures at the end-of-treatment visit (Day 7) and were withdrawn at that time point, not returning for the test-of-cure visit (Day 14).*

*Also, review of the table of "Summary of Discontinuation Reasons" reveals that seven and one subjects discontinued the study in the miconazole nitrate and vehicle groups, respectively, due to being "lost-to-follow-up." Presumably, if caretakers were discontinuing vehicle-treated children because of treatment failure, the numbers of subjects lost-to-follow-up would have been higher in general in the vehicle group, and the numbers of vehicle-treated subjects lost-to-follow-up would have been higher than miconazole-treated (but the reverse is true). Thus, the reviewer considers it likely that the discontinuations for "Clinical Failure/Worsening/No improvement" were investigator-driven and not caretaker-driven. It is also noted that only three subjects discontinued due to withdrawal of consent: one subject was in the miconazole group, and two were in the vehicle group.*

*Because the LOCF approach was followed, clinical failures at Day 7 were considered as treatment failures at Day 14, having failed to meet one of the elements of the primary endpoint. This approach had the ultimate effect of favoring miconazole nitrate because far more subjects*

were discontinued from the vehicle group than were discontinued from the miconazole nitrate group.

The statistical reviewer performed sensitivity analyses to evaluate the robustness of the applicant's efficacy results. Specifically, the following analyses were performed (p.16 of the statistical review):

- a. "Comparison of treatments based on the patients who had data on Day 14.
- b. "Impute missing based on the response rate of patients having data in the respective group."

In these analyses, the efficacy outcomes for the primary endpoint, Overall Cure, were analyzed for subjects who were actually observed at Day 14, (test-of-cure visit), and dropouts were handled as those who remained in the trial, respectively:

**Statistical Reviewer's Table E.1: Comparison of Overall Cure Rate on Day 14 – Study BT100**

Imputation	Miconazole	Vehicle	Comparison
LOCF (or treatment failure)	26/112 (23%)	12/124 (10%)	0.005 <sup>a</sup>
Observed cases	26/98 (26.5%)	12/59 (20.3%)	0.406 <sup>a</sup>
Imputing missing based on the observed cure rate	30/112 (26.8%)	25/124 (20.2%)	0.281 <sup>b</sup>
<b>Source:</b> Table 6 in this review and sponsor's data sets at \\cdsesub\21026\21_000\Hpbio\NDA_21-026\BT100-USA-001.			
<sup>a</sup> p value from CMH test adjusting for investigational group.			
<sup>b</sup> p value from Fisher's exact test.			

The results of the sensitivity analyses indicate that the applicant's data were sensitive to the imputation methods used, as miconazole nitrate was not superior to vehicle in either of these analyses for the primary endpoint, "Overall Cure."

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**Statistical Reviewer's Table A.9: Subgroup Results of Observed Overall Cure Rate on Day 14 by Demographics (MITT) – Study BT100**

Subgroup (Observed results)	Miconazole (n = 112)	Vehicle (n = 124)	Missing (Micon., Vehicle)
Overall	26/98 (26.5%)	12/59 (20.3%)	(14, 65)
Gender			
Male	14/43 (32.6%)	7/29 (24.1%)	(8, 28)
Female	12/55 (21.8%)	5/30 (16.7%)	(6, 37)
Race			
White	6/20 (30%)	2/9 (22.2%)	(4, 25)
Black	1/10 (10%)	0/2 (0%)	(4, 6)
Hispanic/Latino	16/65 (24.6%)	10/46 (21.7%)	(5, 30)
Asian/Pacific Islander	NA	NA	NA
American/Alaska Native	0	0/1 (0%)	(0, 0)
Other	3/3 (100%)	0/1 (0%)	(1, 4)
Age			
Age < 3 months	3/21 (14.3%)	2/10 (20%)	(1, 7)
3 ≤ age < 6 months	6/18 (33.3%)	3/16 (18.8%)	(3, 11)
6 ≤ age < 12 months	14/41 (34.1%)	4/18 (22.2%)	(8, 28)
12 ≤ age < 24 months	3/18 (16.7%)	2/12 (16.7%)	(1, 14)
24 ≤ age < 36 months	NA	1/3 (33.3%)	(1, 5)
age ≥ 36 months	NA	NA	NA
<b>Source:</b> Sponsor's electronic data sets at \\cdsesub\21026\000\Hpbio\NDA_21-026\BT100-USA-001.			

*Comment: 1) The statistical reviewer performed the above subgroup analyses only on the observed cases, i.e. on subjects who had data for the test-of-cure visit, Day 14. This was done to avoid having missing data imputations in the subgroup analyses. Males had higher rates for "Overall Cure" in both treatment groups. "Overall Cure" rates were the same in the oldest age range that had subjects enrolled in both treatment groups. 2) There were eleven subjects in the two-to-four weeks age range, six of whom received treatment with miconazole nitrate, and five of whom received vehicle. No miconazole-treated subjects achieved "Overall Cure": five subjects were failures at Day 14, and data were missing at Day 14 for the remaining subject. One vehicle-treated subject achieved "Overall Cure," and the Day 14 data were missing for the other four vehicle-treated subjects.*

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**Statistical Reviewer's Table A.10: Subgroup Results of Observed Overall Cure Rate on Day 14 by Baseline Characteristics (MITT) – Study BT100**

Subgroup (observed results)	Miconazole (n = 112)	Vehicle (n = 124)	Missing (Micon., Vehicle)
<b>Overall</b>	26/98 (26.5%)	12/59 (20.3%)	(14, 65)
<b>Location</b>			
U.S. Sites	10/35 (28.6%)	4/16 (25%)	(10, 38)
Non-US sites	16/63 (25.4%)	8/43 (18.6%)	(4, 27)
<b>Diaper Dermatitis Severity Index Score</b>			
3	2/6 (33.3%)	3/7 (42.9%)	(3, 8)
4	10/30 (33.3%)	3/17 (17.6%)	(1, 15)
5	11/31 (35.5%)	5/22 (22.7%)	(7, 16)
6	2/16 (12.5%)	1/9 (11.1%)	(2, 13)
7	1/10 (10%)	0/4 (0%)	(1, 9)
8	0/5 (0%)	NA	(0, 4)
<b>Baseline Severity of Diaper Rash</b>			
Mild (score 3-4)	12/36 (33.3%)	6/24 (25%)	(4, 23)
Moderate (score 5-8)	14/62 (22.6%)	6/35 (17.1%)	(10, 42)
<b>Baseline <i>Candida</i> Positive</b>			
<i>Albicans</i>	26/95 (27.4%)	12/57 (21.1%)	(14, 64)
Species other than <i>albicans</i>	0/3 (0%)	0/2 (0%)	(0, 1)
<b>Type of Diaper Used</b>			
U.S. – disposable	10/35 (28.6%)	4/16 (25%)	(10, 38)
Non-U.S.			
Disposable	2/22 (9.1%)	2/14 (14.3%)	(1, 10)
Disposable/Cloth	14/41 (34.1%)	6/29 (20.7%)	(3, 17)
<b>Source:</b> Sponsor's electronic data sets at \\cdsesub\21026\1_000\Hpbio\NDA_21-026\BT100-USA-001.			

*Comment: From the table above, all subjects enrolled from U.S. sites used disposable diapers, and more subjects from the non-U.S. sites used a combination of disposable and cloth diaper than used disposable diapers exclusively. This suggests that diaper use practices may differ between the U.S. and in the non-U.S. countries selected for conduct of the trial. This could raise a question as to the applicability of the data from the non-U.S. to the U.S. population. However, it is probably helpful to have such data, as there may be some users of disposable and cloth diapers in the U.S. who might become users of the applicant's product. Also, if use of both disposable and cloth diapers reflects a common practice in Latin America, it is possible that those practices may be seen more broadly in the U.S., given the growing Hispanic population.*

**Statistical Reviewer's Table A.11: Mean Number of Diaper Changes Per Day – Study BT100**

Country	Type of Diaper	Overall Cure <sup>a</sup> on Day 14?	Miconazole		Vehicle	
			n	Mean (s.d.) range	n	Mean (s.d.) range
U.S.	Disposable	Yes	10	10.1 (4.3) 6 – 20	4	8.0 (2.8) 6 – 12
		No	25	7.5 (2.5) 4 – 15	12	8.0 (2.6) 6 – 15
Non-U.S.	Disposable	Yes	2	8.5 (2.1) 7 – 10	2	4.0 (0) 4 – 4
		No	20	5.6 (2.4) 3 – 12	12	6.2 (1.9) 4 – 10
	Disposable/Cloth	Yes	14	11.9 (5.0) 6 – 20	6	19.0 (7.0) 12 – 30
		No	27	14.3 (6.7) 5 – 30	23	14.5 (9.0) 4 – 36

**Source:** Sponsor's electronic data sets at \\cdsesub\21026\000\Hpbio\NDA\_21-026\BT100-USA-001.  
<sup>a</sup> Patients with observed overall cure data on Day 14.

*Comment: 1) Mean number of diaper changes for miconazole-treated subjects was higher for subjects who were users of disposable diapers who achieved Overall Cure when compared to vehicle-treated subjects who achieved Overall Cure. Mean number of diaper changes was also higher for miconazole-treated subjects who were users of disposable diapers who achieved overall cure at Day 14 when compared to vehicle-treated subjects who did not achieve overall cure. It is possible that the higher mean number of diaper changes by the miconazole-treated subjects contributed to efficacy by keeping a drier diaper environment. 2) When compared within each subgroup of "U.S. disposable," "Non-U.S. disposable, and "Non-U.S. disposable/cloth," mean number of diaper changes was similar for subjects who did not achieve "Overall Cure," irrespective of treatment group. 3) Mean number of diaper changes was higher for both treatment groups for subjects who used both disposable and cloth diapers. This may be due to the caregiver being more readily prompted by the need for a diaper change when using cloth diapers (moistness is more readily detectable through a cloth diaper) 4) Mean numbers of disposable diaper changes were lower generally lower for non-U.S. sites and were lower for all outcomes when like treatment groups were compared between non-U.S. subjects U.S. subjects.*

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**Statistical Reviewer's Missing Data Rates BT 100: U.S. compared to Latin sites**

	0.25% Miconazole Nitrate Ointment	Vehicle
U.S. sites	10/45 (22%)	38/54 (70%)
Non-U.S. sites	4/67 (6%)	27/70 (39%)

Source: p. 16 of the statistical review

*When all missing data were considered (i.e. not just the clinical failures), the missing data rates were higher for the U.S. than for the non-U.S. sites. It is possible that cultural elements may have been at play.*

**Follow-up Telephone Contact at Study Day 28**

This contact was to address the issue of possible recurrence of rash after the test-of-cure visit. For miconazole-treated subjects in the MITT population who achieved "Overall Cure," 25 of 26 (96%) reported no diaper rash at Day 28, and one subject of 26 (4%) reported recurrence on diaper rash (the outcome for one subject was unclear). For vehicle-treated subjects in the MITT population who achieved "Overall Cure," 11 of 12 (92%) had no diaper rash at Day 28.

*Comments: Data from this time point would have been more meaningful had the subjects returned to the study sites for assessment by specified criteria. It is unclear what criteria a caregiver might have applied to diagnose recurrence. Also, it is not clear that caregivers could diagnose candidiasis.*

**Supportive Studies**

Three previously conducted Phase 3 trials were referenced in support of the re-submission:

- 10833/10842.33 (November 1983-June 1984)
- 12966.37A (February 1989-March 1990)
- 12966.37B (December 1988-November 1989)

Data from study 10833/10842.33 were submitted and data from 12966.37A and 12966.37B were included in the original submission of NDA 21-026. The data from these trials were determined to be inadequate to support approval of the respective NDA's. The reviewing Medical Officer for NDA 21-026 concluded that, "(b)ecause of the lack of proper study design (inadequate sample size, lack of microbiologic data, lack of distinction between *C. albicans* infection and colonization, and questionable scales for diseases severity), the phase 3 studies are inadequate to support efficacy." b(4)

**Study 10833/10842.33 (November 1983-June 1984)**

Data from the studies conducted under this protocol were submitted in support of diaper dermatitis. The Medical Officer's review of NDA describes the data as being b(4)

b(4)

from two, single-center, single-investigator studies; the applicant describes these data as being from one study conducted by two investigators (Integrated Summary of Efficacy: Section 8.7 and Table of Studies, Appendix A). As the only other clinical data described in the review of NDA were from topical safety studies, this reviewer considers that the data were likely originally submitted as being from two, single-center, single-investigator studies, since there would otherwise have been only one efficacy study submitted in NDA . However, the data will be discussed as if from a single-study, since all of the data appears to be presented in that format in the resubmission. Additionally, the Medical Officer's review of NDA presents some of the data in a combined fashion (namely the culture data). The data are discussed as a single study in the Medical Officer's review of NDA 21-026.

This study was conducted with the original formulation, 610-58,

(Note: It is acceptable for the applicant to submit these data in support of efficacy since the new formulation removes the ). The study compared formulation 610-58 with the ointment base. Treatment duration was 7 days, and subjects were evaluated on Days 1, 3, 5, and 7; there was no post-treatment assessment such as was done in study BT 100 (at Day 14). Subjects were required only to have a clinical presentation consistent with diaper dermatitis and not the complication of candidiasis. Clinical signs were assessed at each visit, and an overall investigator's rating was performed on a dynamic scale.

While cultures for *Candida albicans* were obtained at baseline from areas of dermatitis (and from the anal area), the results were not a basis for determining study eligibility. Further, microscopic evaluations were not done; therefore, it is not possible to know whether the positive cultures represented infection or colonization. In the Integrated Summary of Efficacy (Volume 16, Section 8.7.2, p.3596), the applicant indicates that the objective of this study was to evaluate the efficacy of their product compared to vehicle in the treatment of acute infantile diaper dermatitis. "A secondary objective was to determine the prevalence of *Candida albicans* associated with diaper rash and the influence of *Candida albicans* on diaper rash severity."

According to the Medical Officer's review of the original submission of NDA 21-026, 107 subjects were enrolled in the study. The following table is based on data extracted from the table on p. 15 of the Medical Officer's review of the original submission of NDA 21-026. Approximately one third of study subjects cultured positive for *Candida albicans* at baseline:

	0.25% Miconazole Nitrate Ointment N= 53	Vehicle N=54
<b>Dermatitis culture positive for <i>Candida albicans</i> at baseline</b>	17 (32%)	19 (35%)
<b>Dermatitis culture negative for <i>Candida albicans</i> at baseline</b>	34 (64%)	35 (65%)
<b>No data</b>	2 (4%)	0 (0%)

The statistical review includes summary of the findings from the original statistical review of February 29, 1999 (Note: It is not clear why the numbers differ from those in the Medical Officer's review):

Statistical Reviewer's Table 2: Number (%) of Patients for Efficacy Endpoints on Day 7 – Study 10833/10842.33

Efficacy endpoint	Patients with <i>Candida albicans</i> at baseline			Patients without <i>Candida albicans</i> at baseline		
	Active (n = 23)	Vehicle (n = 23)	p-value <sup>b</sup>	Active (n = 30)	Vehicle (n = 31)	p-value <sup>b</sup>
<b>Total Rash Score = 0</b>	8 (35%)	3 (13%)	0.087	20 (67%)	19 (61%)	0.665
<b>Overall Rating by Investigator<sup>a</sup></b>			0.014			0.940
Cured	8 (35%)	3 (13%)		20 (69%)	20 (67%)	
Improved	9 (39%)	5 (22%)		5 (17%)	6 (20%)	
No change	1 (4%)	4 (17%)		0	1 (3%)	
Worse/recurred	5 (22%)	11 (48%)		4 (14%)	3 (10%)	
<b>No <i>Candida albicans</i></b>	12 (52%)	3 (13%)	0.064	NA	NA	NA

**Source:** Data summary is based on the Statistical Review (dated 2/29/1999), Tables A.1.3, A.1.4, A.1.8, A.1.9, and A.1.10.  
<sup>a</sup> The overall rating by investigator for patients without *Candida albicans* at baseline was based on 29 and 30 patients in the respective group. One in each group had a missing measurement.  
<sup>b</sup> p values were from Mantel-Haenszel chi-square test.

Miconazole trended towards superiority to vehicle for total clearing of the rash in subjects who had positive cultures for *Candida albicans* at baseline. However, it is unclear whether the positive culture represented actual infection or colonization. Thus, for subjects who had a positive baseline culture, the nature of the “rash” that resolved is unclear. In both treatment groups, subjects with negative baseline cultures had better clinical outcomes (i.e. rash score of 0) than subjects with positive baseline cultures.

This study did not include a post-treatment assessment as was done in BT100 at Day 14. It is possible that the clearance rates would have been higher at a post-treatment reflecting continued resolution of clinical signs.

The extent to which this study population reflects the patient population the applicant currently proposes to treat, i.e. the population of subjects with diaper dermatitis complicated by candidiasis, is unclear. This study was not designed to support the current proposed indication of “treatment of diaper dermatitis complicated by candidiasis.” Therefore, it is unclear to what extent data from this trial could support efficacy of the product for the proposed indication.

Study 12966.37A (February 27, 1989-March 21,1990)

This was a randomized, double-blind, parallel, single-investigator study. The control group was zinc oxide/white petrolatum. That it is a single-investigator trial might limit its usefulness as an “adequate” study. This study was entitled, “An evaluation of the efficacy of BPC Formula No. 610-73 in treatment of acute diaper dermatitis in infants and prevention of onset of severe diaper dermatitis.” Thus, the current formulation was evaluated in this study. The stated objectives were to evaluate the comparative efficacy of the product to ointment base in the treatment of acute dermatitis in infants and in the prevention of the onset of severe diaper dermatitis and to assess the role of *Candida*. Treatment duration was 7 days, and subjects were evaluated on Days 1, 3, 5, and 7; there was no post-treatment assessment such as was done with study BT 100. Cultures were obtained rectally and from the periphery of the rash on Days 0 and 7. However, there were no microbiological criteria for determination of study eligibility. The

following table is based on data are extracted from the table on p. 20 of the Medical Officer's review of the original submission of NDA 21-026:

	0.25% Miconazole Nitrate Ointment N= 101	Vehicle N=101
<b>Dermatitis culture positive for <i>Candida albicans</i> at baseline</b>	30 (30%)	35 (35%)
<b>Dermatitis culture negative for <i>Candida albicans</i> at baseline</b>	71 (70%)	66 (65%)

The statistical review includes summary of the findings from the original statistical review of February 29, 1999 (Note: It is not clear why the numbers differ from those in the Medical Officer's review):

Statistical Reviewer's Table 3: Number (%) of Patients for Efficacy Endpoints on Day 7 – Study 12966.37A

Efficacy endpoint	Patients with <i>Candida albicans</i> at baseline			Patients without <i>Candida albicans</i> at baseline		
	Active (n = 28)	Vehicle (n = 35)	p-value <sup>b</sup>	Active (n = 73)	Vehicle (n = 66)	p-value <sup>b</sup>
<b>Total Rash Score = 0</b>	18 (64%)	2 (6%)	0.001	38 (52%)	28 (42%)	0.258
<b>Overall Rating by Investigator</b>			0.001			0.112
Cured	18 (64%)	4 (11%)		39 (53%)	29 (44%)	
Improved	4 (14%)	7 (20%)		15 (21%)	11 (17%)	
No change	0	8 (23%)		8 (11%)	10 (15%)	
Worse/recurred	6 (21%)	16 (46%)		11 (15%)	16 (24%)	
<b>Global Clinical Impression</b>			0.001			0.145
None	18 (64%)	3 (9%)		39 (53%)	29 (44%)	
Mild	7 (25%)	8 (23%)		28 (38%)	26 (39%)	
Moderate	2 (7%)	17 (49%)		5 (7%)	10 (15%)	
Severe	1 (4%)	7 (20%)		1 (1%)	1 (2%)	
<b>No <i>Candida albicans</i><sup>a</sup></b>	26 (93%)	6 (18%)	0.001	NA	NA	NA

Source: Data summary is based on the Statistical Review (dated 2/29/1999), Tables A.2.3, A.2.4, A.2.8, A.2.9, A.2.11, A.2.12 and A.2.12.  
<sup>a</sup> One patient in vehicle group did not have data on *Candida* culture.  
<sup>b</sup> p values were from Mantel-Haenszel chi-square test.

Miconazole nitrate was superior to vehicle for total clearing of the rash in subjects who had positive cultures for *Candida albicans* at baseline. Clinical cure rates may have been higher at a post-treatment time point. Most subjects in both treatment groups were culture negative (rash) at baseline, and there is a question whether those subjects who were culture positive actually had infection (as opposed to cultures representing colonization.).

Similar to study 10833/10842.33, this study was not designed to support the current proposed indication. See comments regarding study 10833/10842.33

Study 12966.37B (December 7, 1988-November 10, 1989)

This study was of the similar design to 12966.37A except that microbiological data were not collected in this study. Therefore, this study was not designed to support the applicant's proposed indication.

#### 6.1.5 Clinical Microbiology

The applicant was aware that the resubmission should include information that addressed the potential for the development of resistance with use of their product. Pertaining to this issue, advice given to the applicant by the clinical microbiology reviewer included that,

“...it is critical that baseline cultures for yeast be done and that cultures be done in the case of any clinical failure to determine if the reason for failure was development of resistance to miconazole.”  
(October 7, 2002 Guidance Meeting)

An increase in the minimum inhibitory concentration's (MIC) in the post-treatment cultures would suggest the development of resistance. While the applicant did obtain post-treatment cultures, the MIC data for those cultures do not appear to have been included in the resubmission. These data were requested from the applicant during the review cycle.

In vitro susceptibility testing of pre-clinical isolates of *C. albicans* by the applicant showed that 99% of *C. albicans* tested were inhibited by a miconazole concentration of 10 ug/mL. In vitro susceptibility testing of *C. albicans* isolates obtained during clinical study BT 100 showed that 99% of the isolates had miconazole nitrate MICs of <0.06 ug/mL. This data suggests that a concentration of 0.25% miconazole nitrate in the applicant's product should be sufficient to inhibit *C. albicans* that are present at the site of diaper dermatitis.

In Section 2.3.P.4, the applicant describes that the miconazole nitrate concentration of 0.25% w/w was chosen based on the results of two *in vitro* studies in which miconazole nitrate-impregnated and zinc oxide-impregnated agar plates were inoculated with *C. albicans*. The 0.25% concentration was the lowest concentration that showed 100% inhibition of *C. albicans* in both studies. The zinc oxide-impregnated agar plates showed -1.5% inhibition in one study and 12.1% inhibition in the other study of *C. albicans* growth. These data suggest that zinc oxide has no significant activity against *Candida albicans*.

The zinc oxide:miconazole nitrate ratio of 60:1 was based on the results from two additional *in vitro* studies.

#### 6.1.6 Efficacy Conclusions

Miconazole nitrate ointment was superior to vehicle in the treatment of diaper dermatitis complicated by candidiasis in study BT 100 USA/001. By regulatory agreement, the applicant conducted only one study. Also, by agreement, the applicant was required only to demonstrate the contribution of miconazole nitrate to efficacy of their combination product.

The rate of dropouts from the vehicle arm was substantially higher than from the miconazole arm. There was no significant difference in baseline disease characteristics in the treatment groups. The numbers were driven by subjects who were discontinued for being “clinical

failures.” That the discontinuations were more investigator-driven than caregiver-driven is suggested by how few discontinuations were attributed to subjects being “lost-to-follow-up” or for withdrawal of consent, caregiver-driven factors. More vehicle-treated subjects were clinical failures at the end-of-treatment (Day 7) assessment than were miconazole-treated subjects. Therefore, discontinuing subjects at this visit disproportionately affected the vehicle group at the test-of-cure visit (Day 14). None of the subjects who were discontinued for being clinical failures were reported by investigators to have had test-of-cure visits, which with the last-observation-carried-forward analysis, made them treatment failures at test-of-cure. The scenario suggested by the data was that most of these subjects reported for the end-of-treatment visit, were assessed as clinical failures, and discontinued from the study, not reporting for the test-of-cure visit. At discontinuation, vehicle-treated subjects tended to show slight improvement or no change from baseline, i.e. their conditions did not appear to have worsened. That more vehicle-treated subjects were clinical failures at the end-of-treatment could be considered as indirect supportive evidence of efficacy of the applicant’s product for the proposed indication.

The protocol allowed for investigators to withdraw subjects based on clinical judgment. Specifically, subjects could be withdrawn if, “the dermatological symptoms have ‘worsened’, that is, the diaper dermatitis severity index score has increased as compared to baseline evaluation, or that insufficient progress has been made regarding resolution of the symptoms.” The protocol defined “clinical failure as a “diaper dermatitis severity score of greater than 0.” Thus, investigators had wide latitude in deciding when to consider a subject to be a clinical failure.

For miconazole-treated subjects who were clinical failures at the end-of-treatment visit and retained in the study, the reviewer considers that the diaper dermatitis severity scores were sufficiently low (generally 1 -2 or “pink” or “moderate” erythema, respectively) to make this a reasonable clinical decision. “Overall Success” rates for miconazole-treated subjects may have been lower had such subjects been discontinued at end-of-treatment. However, there would have been no strong rationale for this approach, given the generally relatively low severity scores at end-of-treatment for this group.

Similarly, for vehicle-treated subjects who were discontinued from the study on the basis of being clinical failures, the severity scores were sufficiently high (generally at least 4) to make this a reasonable clinical and ethical judgment. This is considered to be particularly true in light of the study population being infants and toddlers. (Note: A score of 4 would require some combination of erythema and papules/pustules or erosions, or a score of 4 would require > 40 papules/pustules.) It cannot be known how many of these discontinued subjects might have improved to achieve “Overall Success” at the test-of-cure visit (at least two vehicle-treated subjects who had severity scores of 4 at the end-of-treatment visit, were clinically clear one week later at the test-of-cure visit). However, it is difficult to fault investigators who discontinued subjects who had the scores that the discontinued subjects tended to have.

That there was no significant difference in the comparison of the “Overall Success” rates when only observed cases were evaluated (i.e. only subjects who had data at the test-of-cure visit), could reflect that vehicle-treated subjects who continued to the test-of-cure visit generally had lower severity scores than vehicle-treated subjects who discontinued the study prematurely, i.e. their eruptions were generally less severe than subjects who discontinued.

The mycological cure rates demonstrate the contribution of miconazole to efficacy to a level of statistical significance when the applicant’s product is compared to vehicle. Even were there

some problem with the handling of specimens that impacted viability of the specimens for culture (making for negative culture results), both treatment arms would have been impacted.

The data also suggest that for users of disposable diapers, the population that may be most relevant to that of U.S., the frequency of diaper changes may contribute to success, since miconazole-treated subjects who achieved "Overall Success" had more frequent changes than vehicle-treated subjects at U.S. and non-U.S. sites. For both treatment groups, some measure of efficacy may have been a function of the increased attention to the diaper environment as a result of participation in the study. Frequent diaper changes are an integral part of treatment for diaper dermatitis, whether complicated by candidiasis or not.

Because the applicant's other three Phase 3 studies were not designed to evaluate the product for the currently-proposed indication, those studies provide limited supportive evidence of efficacy. The primary deficiency with all of those studies was that the presence of candidal infection at baseline was not adequately established (one study included no microbiological assessments). Therefore, it is not clear that similar disease states are being compared across studies. While important, clinical clearing does not speak to microbiological eradication. A negative end-of-treatment culture for a subject who was positive at baseline is not sufficient evidence of the contribution of the antifungal, because, as stated, the presence of candidal infection at baseline was not established. Also, the numbers of subjects were small.

The only study in the applicant's development program designed to support the proposed indication of "treatment of diaper dermatitis complicated by candidiasis," was BT 100 USA/100, submitted in the resubmission. Thus, the sponsor is primarily relying on evidence from one efficacy study to support approval; however, by regulatory agreement the applicant only needed to conduct one study.

## **7 INTEGRATED REVIEW OF SAFETY**

### **7.1 Methods and Findings**

The source for the safety data was the information submitted in the resubmission. There were no assessments that were specified identified as "safety assessments" per se in study BT1000; however, clinical assessments were performed at each study visit, and adverse event data were collected.

#### **7.1.1 Deaths**

There were no deaths reported in the studies conducted in development of the product for the pediatric population. However, in the Integrated Summary of Safety (Section 8.8.9.1), the applicant reports that six deaths occurred during study MIC-BEL-1, conducted in Belgium by Janssen Research Foundation to evaluate the efficacy of 0.25% miconazole nitrate ointment in the treatment of dermatitis in the perineal skin of elderly, hospitalized subjects. At the time of death, three subjects were being treated with 0.25% miconazole nitrate ointment, and three were being treated with the vehicle control. Relationship of all deaths to use of the study medication was reported as doubtful or not drug-related. These subjects are presented in the following table:

Subj. ID #	Age/Gender	Cause of death	Relationship to study drug
4	64/female	Cardiac and respiratory arrest	doubtful
17	73/male	Cardiac failure and Respiratory insufficiency	doubtful
38	72/male	Cardiac arrhythmia	doubtful
2	97/female	Cardiac arrest	doubtful
23	83/female	Pneumonia	not related
46	87/female	Gastric adenocarcinoma	not related

A miconazole-warfarin interaction was reported in the periodic safety update report for miconazole (August 15, 2001 to August 14, 2002) prepared by Johnson & Johnson Pharmaceutical and Research Development, L.L.C. The subject died, and a discussion of this subject follows. A 79-year-old male with multiple medical problems [history of deep venous thrombosis (DVT), cerebrovascular accident (CVA), coronary artery bypass graft, Parkinson's disease, neurogenic bladder, chronic ischemic heart disease, myocardial infarction, pneumonia and rash] was enrolled in a clinical trial (the nature of the clinical trial is unclear). The subject was diagnosed with DVT and was put on heparin and warfarin. Two days later, the subject developed right side facial drop and right side paralysis. Concomitant medications included miconazole cream, quetiapine, acetaminophen, carbidopa/levodopa, metronidazole and furosemide. Warfarin and heparin therapies were discontinued, and the subject was withdrawn from the trial. He suffered a CVA from which he recovered, but ultimately died, reportedly due to progression of his Parkinson's disease. The author did not attribute miconazole to having played a part in the subject's CVA or death, but felt that there might have been a temporal association. It was also indicated that causality could not be determined because of the multiple medical problems and concurrent medications.

#### 7.1.2 Other Serious Adverse Events

No serious adverse events were reported for the 835 subjects participating in the four Phase 3 trials or for the 24 infants in the open-label, absorption study. One of 283 subjects in the topical safety studies was hospitalized for hernia surgery.

A 69-year-old female in study MIC-BEL-1 suffered acute cardiac decompensation. She was being treated with nicardipine and clonidine for hypertension, and intermediate-acting and rapid-acting insulin for diabetes. The subject recovered after five days. Topical treatment with miconazole nitrate was continued. The relationship of the adverse event to the study medication was considered doubtful.

### 7.1.3 Dropouts and Other Significant Adverse Events

No miconazole nitrate-treated subjects discontinued any of the four Phase 3 studies because of an adverse event. No subject discontinued the open-label, uncontrolled absorption study due to an adverse event.

#### 7.1.3.1 Overall profile of dropouts

Four vehicle-treated subjects discontinued the Phase 3 studies because of adverse events (Vol. 17 p.3763 of ISS):

#### Discontinuations due to Adverse Events

Study	Subject #	Discussion/Comment
12966.37A	402-068	Infant experienced mild vomiting, severe diarrhea and worsening diaper dermatitis reported on Day 3; withdrawn on Day 4; diagnosis: gastroenteritis; investigator considered it to be unrelated intercurrent illness
12966.37B	403B-013	Infant had intertrigo at enrollment which had extended by Day 3; study product d/c'd Day 4; withdrawn on Day 5; eruption was considered to be of uncertain relationship to study medication
12966.37B	403B-026	Severe erythema multiforme and swelling of hands and feet; onset and withdrawal in relation to study not provided; subject had receive DPT vaccine two days prior to onset of events; investigator considered the events to have a "possible" relationship to study product
BT100 USA/001	352	Scabies; investigator considered the event "unrelated" to study medication

A summary of the discontinuations from the new study, BT100, is presented in the table below.

#### Summary of Discontinuation Reasons-All Subjects BT100 USA/001, (Sponsor Table 10.1.2 CSR); p. 111

	0.25% Miconazole Nitrate Ointment	Vehicle	Total
Total Number of Subjects Randomized	166	164	330
Completed Test-of-Cure Visit			
Yes	108	66	174
No	58	98	156
Primary Reason for Discontinuation			
Negative Baseline Culture for Candida	45	34	79
Clinical Failure/Worsening/No improvement	4	59	63
Adverse Event	0	1*	1
Subject Withdrew Consent	1	2	3
Protocol Violation	1	1	2
Lost to Follow-up	7	1	8

\*This subject discontinued the study due to scabies; see preceding table

**Applicant Integrated Summary of Safety Table 4: Summary of All Subject Discontinuations in Phase 3 Efficacy Studies\***

	Active Treatment N=418	Vehicle Control N=417	Overall N=835
Clinical Failure/Worsening/Lack of Improvement/Parent Request	9	79	88
Adverse Event	0	3*	3
Subject Withdrew Consent	2	3	5
Protocol Violation	5	2	7
Lost to Follow-Up	7	3	10
Subtotal of ITT <sup>a</sup> and BT100 USA/001 MITT <sup>b</sup> Subjects	23	90	113
Negative Baseline Culture (applies to BT100 USA/001 only)	45	34	79
Total	68	124	192

a ITT=all subjects randomized and dispensed study drug in Studies 10833/10842.33, 12966.37A and 12966.37B

b MITT=all subjects randomized and dispensed study drug with positive baseline culture in Study BT100 USA/001

\* See above table of "Discontinuations due to Adverse Events"; a 4<sup>th</sup> subject was withdrawn because of an adverse event due to parental request (worsening intertrigo;403B-013)

Three subjects discontinued from the Repeated Insult Patch Test (Study HRL 83-129) due to events that were unrelated to 0.25% miconazole nitrate ointment:

- One subject discontinued due to a severe tape reaction. Severe erythema was observed at the edges of the patch, suggesting to the investigator that the reaction was due to the bandage tape rather than the test product.
- One subject discontinued due to hospitalization for hernia surgery.
- One subject discontinued due to an illness (cold).

#### 7.1.3.2 Adverse events associated with dropouts

Across the development program, there was no particular pattern or trend seen with the adverse events associated with dropouts. Subject 403B-013 received vehicle treatment and was discontinued from study 12966.37B due to a worsening of intertrigo that was present at enrollment. This subject is further discussed in Section 7.1.5.5.

#### 7.1.3.3 Other significant adverse events

There were no other significant adverse events.

#### 7.1.5 Common Adverse Events

Adverse events were reported for 143 subjects of the 835 subjects (17%) participating in the four Phase 3 studies: 58 of 418 subjects (14%) in the miconazole nitrate ointment group and 85 of 417 subjects (20%) in the vehicle control group. The most common adverse events were infections and infestations (8% for miconazole nitrate ointment, 12% for vehicle),

gastrointestinal disorders (2% for miconazole nitrate ointment, 3% for vehicle), and respiratory, thoracic and mediastinal disorders (3% for miconazole nitrate ointment, 2% for vehicle).

#### 7.1.5.1 Eliciting adverse events data in the development program

In study BT 100, clinical assessments were performed at each visit [Days 0, 3, 5 (optional), 7 and 14]. A telephone contact was made on Day 28 to inquire about recurrence of rash. Additionally, at each study visit, diary sheets were reviewed, and the caregiver was interviewed about adverse events and concomitant medications. The diary sheets, however, allowed only for the recording of application of study product, whether the child was bathed and whether diaper type was changed. The case report form did direct the investigator to fill out an adverse event form if an adverse event were reported at a particular visit.

The methods for eliciting adverse event data in the other Phase 3 trials is unclear.

#### 7.1.5.2 Appropriateness of adverse event categorization and preferred terms

In the new Phase 3 trial, BT100, the applicant classified adverse events using the MedDRA dictionary of preferred terms. At the guidance meeting held July 27, 2004, the applicant proposed to extract safety data from the previous trials and code using MedDRA terminology to permit integration of these data with the new safety data for the Integrated Summary of Safety. The reviewer compared the applicant's categorization of events by preferred terms for BT100 to the terms used by investigators and subjects in the coding/reporting of adverse events. The applicant's coding was generally acceptable when preferred terms were compared with the terms used by investigators in their recording of the event. In integrating the safety data for the integrated summary, adverse events were also mapped to the COSTART dictionary.

#### 7.1.5.3 Incidence of common adverse events

In BT100, most adverse events in both treatment groups were of mild severity: 38 of 53 events (72%) in the miconazole group and 35 of 47 events (75%) in the vehicle group (Table 14.3.1.1). The remaining events in both treatment groups were of moderate severity except for one severe adverse event in the vehicle group (wheezing). The most frequent adverse event reported in both treatment groups involved infections and infestations (12% in the miconazole group and 10% in the vehicle group). Respiratory, thoracic, and mediastinal disorders were reported in 5% of miconazole-treated subjects. Gastrointestinal disorders were reported in 4% of subjects in both treatment groups. The reviewer considers these reports to be consistent with the age group of the study subjects, i.e. infants and young children. All events in the miconazole group were considered unlikely or unrelated to study product; all events in the vehicle group were considered unrelated to study product.

All Phase 3 trials

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Adverse events were reported for 143 subjects of the 835 subjects (17%) participating in the four Phase 3 studies: 58 of 418 subjects (14%) in the miconazole nitrate ointment group and 85 of 417 subjects (20%) in the vehicle control group. The most common adverse events were infections and infestations (8% for miconazole nitrate ointment, 12% for vehicle), gastrointestinal disorders (2% for miconazole nitrate ointment, 3% for vehicle control), and respiratory, thoracic and mediastinal disorders (3% for miconazole nitrate ointment, 2% for vehicle control).

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#### 7.1.5.4 Common adverse event tables

Common adverse event tables follow.

Sponsor Table 14.3.1.1 Summary of Adverse Events by System Organ Class- BT100 USA/001

System Organ Class*	0.25% Miconazole Nitrate Ointment N= 166	Vehicle N=164
Ear and labyrinth disorders	1 (1%)	1 (1%)
Ear discomfort	1 (1%)	0 (0%)
Middle ear infusion	0 (0%)	1 (1%)
Gastrointestinal	7 (4%)	7 (4%)
Abdominal pain	1 (1%)	0 (0%)
Diarrhoea	3 (2%)	5 (3%)
Enteritis	1 (1%)	0 (0%)
Haematochezia	1 (1%)	0 (0%)
Loose stools	1 (1%)	2 (1%)
Oesophagitis	1 (1%)	0 (0%)
Teething	1 (1%)	0 (0%)
Vomiting	1 (1%)	0 (0%)
General disorders and administration site conditions	6 (4%)	5 (3%)
Discomfort	0 (0%)	1 (1%)
Injection site discomfort	1 (1%)	0 (0%)
Pyrexia	5 (3%)	5 (3%)
Infections and infestations	20 (12%)	17 (10%)
Bacterial infection	0 (0%)	1 (1%)
Bronchiolitis	1 (1%)	0 (0%)
Bronchitis	1 (1%)	1 (1%)
Bronchopneumonia	0 (0%)	1 (1%)
Candidiasis	3 (2%)	0 (0%)
Conjunctivitis infective	1 (1%)	0 (0%)
Ear infection	1 (1%)	0 (0%)
Furuncle	1 (1%)	0 (0%)
Gastroenteritis rotavirus	1 (1%)	0 (0%)
Gastroenteritis viral	0 (0%)	1 (1%)
Nasopharyngitis	5 (3%)	6 (4%)
Otitis media	1 (1%)	2 (1%)
Pharyngeal candidiasis	0 (0%)	1 (1%)
Roseola	1 (1%)	0 (0%)
Scabies infestation	0 (0%)	1 (1%)
Tonsillitis	1 (1%)	1 (1%)
Upper respiratory tract infection	3 (2%)	4 (2%)
Viral infection	1 (1%)	0 (0%)
Injury, poisoning and procedural complications	1 (1%)	4 (2%)
Excoriation	0 (0%)	1 (1%)
Face injury	1 (1%)	0 (0%)
Fall	0 (0%)	1 (1%)
Skin laceration	1 (1%)	0 (0%)
Tongue injury	0 (0%)	1 (1%)
Vaccination complication	0 (0%)	1 (1%)
Respiratory, thoracic and mediastinal disorders	9 (5%)	4 (2%)
Asthma	0 (0%)	1 (1%)
Cough	5 (3%)	0 (0%)
Nasal congestion	2 (1%)	1 (1%)
Rhinorrhoea	1 (1%)	2 (1%)
Sinus congestion	1 (1%)	0 (0%)
Upper respiratory tract congestion	1 (1%)	0 (0%)

Clinical Review  
 Brenda Carr  
 NDA 21-026  
 (miconazole nitrate/zinc oxide/white petrolatum)

Wheezing	0 (0%)	1 (1%)
Skin and subcutaneous tissue disorders	1 (1%)	1 (1%)
Erythema	0 (0%)	1 (1%)
Heat rash	1 (1%)	0 (0%)
Rash popular	0 (0%)	1 (1%)

\*Counts reflect numbers of subjects in each treatment group reporting one or more adverse events that may to the MedDRA System Organ Class. At each level of summarization (system organ class or event) subjects are only counted once. Percentages of subjects in each treatment group are also given.

Appendix A.II.5.3.1 ISS\* (p.3848) Summary of Adverse Events-All Phase 3 studies at ≥1%

System Organ Class*	0.25% Miconazole Nitrate Ointment N= 418	Vehicle N=417
Number of Events Reported	78	110
Number of Subjects Reporting One or More Events	58	85 (20%)
Eye disorders	3 (1%)	1 (<1%)
Conjunctivitis	3 (1%)	1 (<1%)
Gastrointestinal	10 (2%)	14 (3%)
Diarrhoea	4 (1%)	9 (2%)
Loose stools	2 (<1%)	3 (1%)
General disorders and administration site conditions	9 (2%)	9 (2%)
Pyrexia	8 (2%)	9 (2%)
Infections and infestations	32 (8%)	52 (12%)
Bronchitis	2 (<1%)	3 (1%)
Candidiasis	3 (1%)	0 (0%)
Nasopharyngitis	8 (2%)	8 (2%)
Oral candidiasis	1 (<1%)	5 (1%)
Otitis media	3 (1%)	7 (2%)
Upper respiratory tract infection	5 (1%)	22 (5%)
Respiratory, thoracic and mediastinal disorders	11 (3%)	7 (2%)
Cough	5 (1%)	0 (0%)
Nasal congestion	3 (1%)	1 (<1%)
Rhinorrhoea	2 (<1%)	4 (1%)

Total number of events in the system organ class; specific events are only reported if they occurred at ≥ 1%.

\*Integrated Summary of Safety

7.1.5.5 Identifying common and drug-related adverse events

There was no consistent difference in the occurrence or types of adverse events when the miconazole nitrate and vehicle groups were compared. Two subjects had reactions that were considered by the investigators to be of “uncertain” relationship to the study product:

- Study 12966.37A: A miconazole-treated infant (Subject 402-010) of unspecified age was reported to have a rash of moderate severity on the face, neck, and chin that began on Study Day 2. The investigator classified the relationship of the rash to the study medication as “uncertain,” stating that the infant had previously experienced an uncomplicated rash. The rash persisted longer than 5 days and was treated with 1% hydrocortisone cream applied twice daily to the affected area. The subject completed the study.
- Study 12966.37B: A vehicle-treated subject (403B-013) had “mild” intertrigo on the neck and axillary creases upon enrollment that was considered related to inadequate drying after bathing. The infant (age?) was prescribed betamethasone valerate cream to be applied twice daily to the neck and axillary creases. At

the Day 3 evaluation, the rash was noted to have extended on the lower abdomen and buttocks. The mother discontinued using the test product on Day 4 and the infant was withdrawn from the study on Day 5 due to parental request. The rash was considered to be of "uncertain" relationship to the study medication. The rash was treated with Nilstat® cream and subsequently was reported to have resolved.

*Comment: It is not clear that a topical corticosteroid was the best choice of treatment for intertrigo, and it is possible that the subject's worsening was a function of the steroid. (It is also not clear that a mid-potency topical corticosteroid was the best choice of treatment for an intertriginous eruption, particularly in an infant). It is noted that the rash resolved following use of Nilstat® cream, which in the U.S., is a discontinued product which had nystatin as the active ingredient. However, studies 12966.37A and B were conducted in Australia.*

One vehicle-treated subject in study 12966.37B developed "severe" erythema multiforme on the feet and hands on Study Day 3. The investigator considered the relationship of the adverse event to the study medication as "possible." The investigator indicated that the infant had been treated previously with zinc oxide ointment without adverse effects. This subject is further described in Section 7.1.3.1.

#### 8.8.7 Adverse Event Incidence Rates for Use in the Proposed Labeling

Review of the safety data indicated that use of 0.25% miconazole nitrate ointment appears to be associated with minimal risk of drug-related adverse events. One of 418 (0.2%) subjects in the active treatment group and two of 417 (0.5%) subjects in the vehicle control group experienced adverse events that might have been related to study treatment. These three subjects are discussed in Section 7.1.5.5. Adverse events in both treatment groups were otherwise recorded as either unlikely or unrelated to study product. There was no consistent difference in the occurrence or types of adverse events when the miconazole nitrate and vehicle groups were compared.

#### 7.1.5.5 Additional analyses and explorations

No additional safety analyses or explorations are thought necessary at this juncture for the infant population. There were no adverse events that appeared to have been drug-related.

#### 7.1.6 Less Common Adverse Events

Events that occurred at a rate  $\geq 1\%$  are presented in Section 7.1.5.4. Review of Appendix A.II.5.3.1, entitled "Summary of Subjects with Adverse Events by MedDRA System Organ Class" (Integrated Summary of Safety) revealed that only one subject was affected for most events that occurred at a rate of  $< 1\%$  occurred. There was no pattern regarding the treatment groups for events that occurred at  $< 1\%$ .

#### 7.1.7 Laboratory Findings

Laboratory testing (chemistry, hematology, and urinalysis) was not conducted in the clinical development program.

#### 7.1.8 Vital Signs

Vital signs were not assessed in the clinical development program.

#### 7.1.9 Electrocardiograms (ECGs)

Electrocardiograms were not done in the clinical development program

#### 7.1.10 Immunogenicity

This section does not apply to the applicant's product.

#### 7.1.11 Human Carcinogenicity

Carcinogenicity studies were not submitted.

#### 7.1.12 Special Safety Studies

The applicant conducted five clinical pharmacology studies four of which were topical safety studies to assess the phototoxic, photoallergenic, allergic and cumulative irritation potential of 0.25% miconazole nitrate. The fifth study was an open-label, uncontrolled absorption study that was conducted in hospitalized infants with diaper dermatitis associated with systemic pathology (see Section 5).

The topical safety studies were conducted with formulation BPC 610-58 which is a different formulation than was used in three of the four Phase 3 trials. The current formulation, 610-73, lacks the \_\_\_\_\_ that was found in BPC 610-58. Therefore, the topical safety studies are acceptable for consideration in support of the safety of 610-73. All of the topical safety studies were conducted in adults. This too is acceptable as it would be ethically problematic to conduct topical safety studies in infants. Also, the skin of infants may be more resistant to contact sensitizers than skin of older children and adults.<sup>5</sup> This makes it reasonable to extrapolate the adult results down to the younger age group, since if no signal for sensitization is seen in adults, it may be even less likely for one to be seen in infants. These studies have been previously reviewed (in the original submission of the application).

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#### Cumulative irritancy

This study enrolled 26 adults. Study subjects received six applications of miconazole nitrate ointment and vehicle under occlusion (48-72 hours per application). No positive reactions were observed in the study in either the group. It was concluded that based on conditions of the study, no evidence of cumulative irritancy was demonstrated.

#### Repeat insult patch test/contact sensitization

This study enrolled 216 adults. During the 3-week induction period, subjects had occlusive patches of study drug applied twice weekly (24 hours per application). Eleven subjects reportedly had reactions graded between “none and 1+ erythema” (five during induction; six during challenge). No subjects had a reaction of 1+ or greater intensity. The applicant’s product was concluded to have a low potential for contact sensitization.

#### Phototoxicity

The study included ten adult subjects. Testing was conducted only with the UV-A wavelength. Based on the conditions of the study, evidence of phototoxicity was not established.

#### Photoallergenicity

This study enrolled 31 adult subjects. While both UV-A and UV-B were used in the induction phase, only UV-A was used in the challenge phase. Based on the conditions of the study, evidence of photoallergenicity was not established.

#### 7.1.13 Withdrawal Phenomena and/or Abuse Potential

This section does not apply to the applicant’s product.

#### 7.1.14 Human Reproduction and Pregnancy Data

The applicant did not provide any information on drug exposure in pregnant women (see Section 8.8.14 of the Integrated Summary of Safety). While the age group for the proposed indication would obviously not be at risk for pregnancy, it is possible that their caregivers could be. Some women who use the product for vulvovaginal candidiasis likely fall within the childbearing age range. Miconazole is in pregnancy category C.

#### 7.1.15 Assessment of Effect on Growth

Assessment for effect(s) on growth were not evaluated.

#### 7.1.16 Overdose Experience

No cases of overdosing have been reported according to applicant (Section 8.8.13 of the Integrated Summary of Safety). However, the applicant did report that a 73-year-old female used an entire bottle of miconazole spray over a period of 2 days. She was reported to have developed a “contact dermatitis and second degree burns over 30% of her body.” Her outcome was not reported.

The applicant also reported 15 cases of accidental ingestion of miconazole topical gel. The reported ages ranged from 5 weeks to 75 years (ages were not provided for all subjects). According to the applicant, no “subsequent adverse events were reported for these 15 cases.” Outcomes were not otherwise provided for these subjects.

#### 7.1.17 Postmarketing Experience

Postmarketing surveillance through September 28, 1989 revealed 40 adverse events in a total of 29 individuals using miconazole dermatological formulations. Most of reactions reported for topical formulations of miconazole nitrate were "local site reactions."

A safety report for period of February 28, 1991 through February 29, 1996 summarized the worldwide safety data as assessed by the Pharmacovigilance Department of Janssen Research Foundation. This report reflected use of various topical miconazole formulations (i.e. cream, powder, lotion and tinctures). Two of the six adverse events reported were classified as possibly related to use of the 0.25% miconazole nitrate ointment:

- A 24-year-old female who developed unspecified erythema while treating her newborn infant with miconazole nitrate ointment. She recovered from the adverse event.
- An infant developed an allergic reaction of unknown origin and etiology after the application of miconazole nitrate ointment (Daktozin®; country of registration is unclear).

The remaining four reported adverse events involved cardiac and respiratory events, as well as a malignancy, and all were considered unrelated to the use of miconazole nitrate. Updated safety reports for the periods of March 1, 1996 to August 14, 2001, August 15, 2001 to August 14, 2002, and August 15, 2002 to August 14 2003 summarized the worldwide safety data as assessed by the Drug Safety & Surveillance Department of Johnson & Johnson Pharmaceutical Research and Development, L.L.C. The applicant concluded that no new relevant safety information was identified from the review of these reports, and no trends were observed in the safety data, and the reviewer agrees. A more recent overview of safety data was not included in the re-submission. Requests for updated information were forwarded to the applicant on February 8, 2005, and on April 6, 2005.

A topical product containing 0.25% miconazole nitrate ointment has been approved for commercial use in 18 countries outside the U.S. The initial approval was received in Belgium in 1991. Johnson & Johnson (Janssen Pharmaceutica) has submitted 26 marketing authorization filings (including the U.S.).

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## 7.2 Adequacy of Patient Exposure and Safety Assessments

### 7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The applicant's submission was the source for the safety data that were reviewed.

Clinical Review  
Brenda Carr  
NDA 21-026  
(miconazole nitrate/zinc oxide/white petrolatum)

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**Modified Sponsor Table from ISS Table 1. All Clinical Studies (Clinical Pharmacology/Phase III) Supporting Safety of 0.25% Miconazole Nitrate Ointment**

Study No. Investigator(s)	Study Title (Study Dates)	Study Design	Treatment	# Subjects (#/Treatment)	Mean Age (Age Range)
83-513T Washlaw	Phototoxicity Test (10/25/83-10/28/83)	open-label	Patch applied to each forearm for 24 hours. One forearm irradiated with UV-A light. <sup>a</sup>	10 (2/8)	N/A (23-60 years)
83-513A Washlaw	Photoallergy Test (10/31/83-12/8/83)	Open-label	Patch applied to each forearm for 24 hours 2x/week for 3 weeks. One forearm irradiated with UV-A & UV-B light after each application. After 10-14 day rest period, challenge patch applied to virgin site of each forearm & one forearm irradiated with UV-A light. <sup>a</sup>	31 (2/29)	N/A (20-63 years)
83-129 Washlaw	Repeated Insult Test/Draize Sensitization Test (12/5/83-1/13/84)	open-label	Patch applied to upper back for 24 hours 3x/week for 3 weeks. After 10-14 day rest period, 2 consecutive challenge patches applied to virgin site of back. <sup>a</sup>	216 (60/156)	N/A (18-68 years)
227,0184 Kantor	Cumulative Irritation Test (1/25/84-2/8/84)	open-label	Patches with active & control product applied to upper back for 48 or 72 hours 3x/week for 2 weeks. <sup>a</sup>	26 (1/25)	N/A (18-65 years)
12966,37C Herrera	Study of Absorption & Efficacy of Miconazole Nitrate in Infants with Diaper Dermatitis Associated with Systemic Pathology (7/19/88-6/14/89)	open-label, uncontrolled, noncrossover	0.25% or 2% miconazole nitrate applied to clinically affected area at each diaper change for 7 days. Blood samples collected before and at the end of treatment. <sup>a</sup>	24 [19, 0.25%, 5, 2%] (12/12)	6.87 months (1-12 months)
10833/10842,33 Manners and Silverman (402)	A Multicenter Evaluation of BPC Formula No. 610-58 in Treatment of Acute Diaper Dermatitis in Infants (11/7/83-6/23/84)	Phase 3, randomized, DB, PCB, parallel	0.25% miconazole nitrate (MN) or vehicle control (VC) applied to clinically affected area at each diaper change for 7 days.	107 [53 MN, 54 VC] (48/59)	7.1 months (1.8-12.0)
12966,37A Concaanon (403A)	An Evaluation of the Efficacy of BPC Formula No. 610-73 in Treatment of Acute Diaper Dermatitis in Infants (2/27/89-3/21/90)	Phase II, Randomized, DB, PCB, parallel	0.25% miconazole nitrate (MN) or vehicle control (VC) applied to clinically affected area at each diaper change for 7 days.	202 [101 MN, 101 VC]	5.7 months (1.7-13.0)
12966,37B Wagner and Lillystone (403B)	A Multicenter Evaluation of the Efficacy of BPC Formula No. 610-73 in Treatment of Acute Diaper Dermatitis in Infants (12/7/88-1/1/0/89)	Phase III, Randomized, DB, PCB, parallel	0.25% miconazole nitrate (MN) or vehicle control (VC) applied to clinically affected area at each diaper change for 7 days.	196 [98 MN, 98 VC] (91/105)	5.8 months (1.7-12.3)
BT100 USA/001 Multiple	A Double-Blind, Randomized, Multi-Center Study of 0.25% Miconazole-Nitrate Ointment in the Treatment of Cutaneous Candidiasis Complicating Diaper Dermatitis(4/3/03-6/30/04)	Phase III, Randomized, DB, multi-center	0.25% miconazole nitrate (MN) or vehicle control (VC) applied to clinically affected area at each diaper change for 7 days.	330 [166 MN, 164 VC] (145/185)	9.16 MN, 9.97 VC (0.4-35.2) Months

<sup>a</sup> 0.2 to 0.3 ml of 0.25% miconazole nitrate ointment (BPC 610-58) applied to an occlusive patch MN = 0.25% miconazole nitrate ointment PCB = Placebo-controlled, Balanced  
b 0.2 to 0.3 ml of 0.25% miconazole nitrate ointment (BPC 610-58) or vehicle control applied to an occlusive patch VC = vehicle control  
c 0.25% miconazole nitrate ointment (Janssen F100) or 2% miconazole nitrate cream DB = Double-blind  
MN = 0.25% miconazole nitrate ointment  
VC = vehicle control  
DB = Double-blind PCB = Placebo-controlled, Balanced

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