DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DATE: May 31, 2000

FROM: Executive Secretary
Dermatologic and Ophthalmic Drugs Advisory Committee

SUBJECT: Background Material for the 30 June 2000 Meeting

TO: Committee Members, Consultants, and Guests

The attached background material is for your review for the next meeting of the Dermatologic & Ophthalmic Drugs Advisory Committee which will be held in Versailles Ballrooms I and II of the Bethesda Holiday Inn, 8120 Wisconsin Avenue. Starting at 8:30 a.m., the **OPEN** sessions will commence.

This meeting session is scheduled to adjourn around 5:30 p.m. DODAC Members and Consultants are reminded that they *must be present* to cast their votes and therefore should make travel plans that allow for participation in the meeting for the entire scheduled time.

I look forward to seeing you. If you have any questions, please call me or Angie Whitacre on 301-827-7001 or e-mail me at RileyT@CDER.FDA.GOV.

Tracy Riley
Executive Secretary

Enclosures

1. FDA briefing documents regarding NDA 21-026
2. Sponsor briefing documents regarding NDA 21-026

# Summary Information on NDA 21-026 for the Dermatologic and Ophthalmologic Drugs Advisory Committee

# Table of Contents


| | | Page |
|---|---|---|
| 1. | Introduction | 4 |
| 1.1. | Diaper Dermatitis | 4 |
| 1.2. | J&J's Miconazole Nitrate 0.25% Ointment | 4 |
| 2. | Regulatory History of J&J's Miconazole Nitrate 0.25% Ointment in the U.S. | 5 |
| 2.1. | IND | 5 |
| 2.2. | NDA | 6 |
| 2.3. | Events Leading to NDA 21-026 | 6 |
| 2.4. | NDA 21-026 | 6 |
| 2.5. | Evolution of Proposed Indication | 7 |
| 3. | Clinical Program in Support of NDA 21-026 | 7 |
| 4. | Efficacy Evaluation | 7 |
| 4.1. | Dose-ranging | 8 |
| 4.2. | Phase 3 Program | 8 |
| 4.2.1. | Similarities among the Phase 3 Trials | 8 |
| 4.2.2. | Differences between the Three Phase 3 Trials | 8 |
| 4.2.3. | Study Design of Phase 3 Trials | 9 |
| 4.2.3.1. | Problems in the Conduct of the Phase 3 Trials | 9 |
| 4.2.3.2. | Problems in Evaluation | 10 |
| 4.3. | Results on Efficacy in Phase 3 Studies | 11 |
| 4.3.1. | Study 10833/10842.33 | 12 |
| 4.3.2. | Study 12966.37A | 12 |
| 4.3.3. | Study 12966.37B | 12 |
| 4.4. | Overview of Efficacy | 12 |
| 4.4.1. | Efficacy for the Indication "Moderate to Severe Diaper Dermatitis where *Candida albicans* may be a Contributing Factor" | 12 |
| 4.4.1.1. | Study 10833/10842.33 | 12 |
| 4.4.1.2. | Study 12966.37A | 13 |
| 4.4.1.3. | Study 12966.37B | 14 |
| 4.4.1.4. | Conclusion on Efficacy for the Indication "Moderate to Severe Diaper Dermatitis where *Candida albicans* may be a Contributing Factor" | 14 |
| 4.4.2. | Efficacy for the Indication "Infants with Diaper Dermatitis" | 14 |
| 4.4.2.1. | Study 10833/10842.33 | 14 |
| 4.4.2.2. | Study 12966.37A | 14 |
| 4.4.2.3. | Study 12966.37B | 15 |
| 4.4.2.4. | Conclusion on Efficacy for the Indication "Infants with Diaper Dermatitis" | 15 |
| 4.4.3. | Efficacy of J&J's Miconazole Nitrate 0.25% Ointment in Diaper Dermatitis of Elderly, Hospitalized Patients | 15 |
| 5. | Safety Evaluation | 15 |
| 5.1. | Dataset/Exposure Information | 16 |
| 5.2. | Adverse Event Data | 17 |
| 5.2.1. | Significant/Potentially Significant Adverse Experiences | 17 |
| 5.2.2. | Adverse Event Table | 17 |
| 5.3. | Dermal Safety Studies | 18 |
| 5.4. | Pharmacokinetics Study | 19 |
| 5.5. | Potential Adverse Effects of Ointment Base | 19 |
| 6. | Resistance | 20 |
| 7. | J&J Responses to Issues in Non-Approvable Letter of 6/28/99 | 20 |
| 7.1. | Demonstration of Efficacy for J&J's Miconazole Nitrate 0.25% Ointment | 20 |

7.2. Target Population in Future Studies 21
7.3. Potential Adverse Effect of Ointment Base 21

8. Summary of Risks and Benefits 22

9. Questions for Discussion 23

Attachments

1. Skin Protectant Drug Products for OTC Human Use (347); Diaper Rash Drug Products Proposed Rule (FR 6/20/90)

2. Topical Antifungal Drug Products for OTC Human Use; Diaper Rash Labeling Claims; Final Rule (FR 12/18/92)

3.

4. Minutes of pre-NDA meeting for INC

5. Non-Approval Letter of 1999 for NDA 21-026

6. Proposed Label for J&J's Miconazole Nitrate Ointment 0.25% (submitted 3/28/00)

7. *Antifungal drug resistance in Candida albicans* by TC White

8. *Clinical, cellular and molecular factors that contribute to antifungal drug resistance* by TC White, KA Marr and RA Bowden

9. *Characterisation of yeasts implicated in vulvovaginal candidosis in Irish women* by N al-Rawi and K Kavanagh

10. *Emergence of resistance of Candida albicans to clotrimazole in human immunodeficiency virus-infected children: in vitro and clinical correlations* by R Pelletier, J Peter, C Antin, C Gonzalez, L Wood and TJ Walsh

11. *Systemic candidiasis in extremely low birth weight infants receiving topical petrolatum ointment for skin care: a case-control study* by JR Campbell, E Zaccaria and CJ Baker

## 1. Introduction

### 1.1. Diaper Dermatitis

"Diaper dermatitis" is a clinical diagnosis but not a single pathophysiologic entity. It may arise primarily as an irritant dermatitis in an occluded area due to irritation from prolonged contact with products in or derived from urine or feces. Hydration and increase in skin pH impairs the barrier function and may render it more susceptible to microbial infection. The increase in skin pH may also increase the activity of the proteolytic and lipolytic enzymes from feces, leading to skin damage. This in turn increases further its susceptibility to other irritants and microbes, including bacteria and fungi. Products derived from microbes may also be potential irritants.

There are several subtypes of diaper dermatitis, one of which is due to secondary *Candida albicans* infection. In infants with diaper rash, recovery of *C. albicans* on skin ranged from 8% (Brookes *et al*) to 77% (Montes *et al*). This recovery rate depends on the population being studied and the location from which the culture was taken. In general, recovery of *C. albicans* is more likely in the more severe cases of diaper dermatitis, which may come to the physician's attention. However, the great majority of cases are milder, and managed by parents with hygienic measures and/or OTC topical therapies. Currently these topical treatments are available under a Proposed Rule published on 6/20/90 (Skin Protectant Drug Products for Over-the-Counter Human Use; Diaper Rash Products; Proposed Rule. See Attachment 1). Antifungals are not considered appropriate for OTC treatment of diaper rash (See Attachment 2 for Final Rule on Antifungal Drug Products for OTC Human Use; Diaper Rash Labeling Claims).

In a Dermatologic Drugs Advisory Committee Meeting dated 11/26/90, the Committee discussed the potential use of antifungal/corticosteroid combination in diaper dermatitis, and unanimously agreed that "diaper dermatitis" was not a defined diagnosis and therefore not an appropriate indication. An indication for "diaper dermatitis" without specifying etiology may be regarded as analogous to an indication for "pneumonia" in which the infecting organism is not specified; as well, there is also the additional component of irritation.

### 1.2. J&J's Miconazole Nitrate 0.25% Ointment

At the time of NDA submission in 1998, J&J's miconazole nitrate 0.25% ointment was approved in 11 countries and marketed in 6 for the treatment of diaper dermatitis. Approval for marketing has been denied in Norway. This ointment has the following composition:

**J&J's Miconazole Nitrate 0.25% Ointment Formulations**

| Ingredient | Formula 610-58 %w/w | Formula 610-73 %w/w |
|---|---|---|
| Miconazole Nitrate, USP | 0.25 | 0.25 |
| Trihydroxystearin | | |
| Zinc Oxide, USP | | |
| | | |
| White Petrolatum, USP | | |

The clinical studies done before 1986 (dermal safety studies and one phase 3 trial) used Formula 610-58 while those done after 1987 used the newer formulation, 610-73, proposed for marketing. The difference lies in the deletion of from the , in the newer formula. This difference should not invalidate studies done with the older formulation, as (a) the newer formulation simply eliminates the use of a for an occluded area, and (b) there is no evidence that has an effect on the safety or efficacy of miconazole.

Miconazole nitrate at a concentration of 0.25% is not a marketed product in the U.S. Miconazole nitrate 2% was approved on 1/8/74 under the tradename Monistat-Derm Cream (Ortho). Currently, miconazole nitrate 2% is OTC-monographed for the treatment of tinea pedis, tinea corporis and tinea cruris (21 CFR333.210(c)), with the provision that it is not to be used on children under 2 years of age unless directed by a doctor (21CFR333.250(c)(1)(i)).

Under the Proposed Rule for diaper rash products of 6/20/90, the concentrations of petrolatum and zinc oxide are allowable when alone or in combination for diaper rash (§347.10(h) and (m) and §347.20(e)). J&J's miconazole nitrate 0.25% ointment is a combination of antifungal and skin protectant, although the effect of petrolatum and zinc is not claimed. While it is acceptable to use an antifungal for an infectious process, its place in the treatment of diaper dermatitis, of which the majority of cases do not involve Candida, would require justification.

2. Regulatory History of J&J's Miconazole Nitrate 0.25% Ointment in the U.S.

2.1. IND

J&J's miconazole nitrate 0.25% ointment was studied under IND
IND as submitted on 2/4/83 with a single-center phase 3 protocol:

- An evaluation of the efficacy of BPC Formula No. 610-58 in the treatment of acute infantile diaper dermatitis and prevention of onset of severe diaper dermatitis (10833/10842.33)

The IND was placed on clinical hold on 3/3/83 because of safety concerns. J&J addressed the concerns and the IND was released from clinical hold on 9/21/83.

By a submission on 1/13/84, J&J added a second Investigator to conduct the above phase 3 protocol.

2.2. NDA

Based on the findings from two centers in the study conducted under IND . , NDA was submitted on for the drug product Therapedia

. J&J held a meeting with FDA on 6/2/86 and considered doing new studies.

Between 12/88 and 3/90, J&J conducted two phase 3 studies in Australia:

- An evaluation of the efficacy of BPC Formula 610-73 in treatment of acute diaper dermatitis in infants and prevention of onset of severe diaper dermatitis (12966.37A)
- An multicenter evaluation of the efficacy of BPC Formula 610-73 in treatment of acute diaper dermatitis in infants and prevention of onset of severe diaper dermatitis (12966.37B)

J&J also performed a pharmacokinetic study in Mexico between 7/88 and 6/89:

- Study of absorption and efficacy of miconazole nitrate in infants with diaper dermatitis associated with systemic pathology (12966.37C)

2.3. Events Leading to NDA 21-026 Submission

J&J held a pre-NDA meeting with the Division of Dermatologic and Dental Drug Products on 1/9/97 and a teleconference with the Chemistry group on 5/22/98. At the pre-NDA meeting, J&J was advised of the need of additional clinical studies to support an NDA submission (see Attachment 4 for minutes). In summary, FDA advised J&J of the following as necessary to win approval for miconazole nitrate in diaper dermatitis:

<u>For diaper dermatitis without Candida involvement -</u>

- evidence that the vehicle is not having a negative effect, thus giving a false impression of effectiveness of the active
- evidence that using an anti-infective in the absence of infection would not give rise to resistant organisms

<u>For diaper dermatitis with Candida -</u>

- demonstration of infection vs. colonization

2.4. NDA 21-026

NDA 21-026 was submitted on 8/24/98 for the drug product PEDIASTAT™ (miconazole nitrate 0.25%) Ointment.
A teleconference was held on 10/20/98 between FDA and J&J to discuss fileability and potential review issues.
NDA 21-026 was filed on 10/23/98.

A non-approvable letter was issued on 6/28/99 (see Attachment 5 for NA letter).
J&J indicated their intention to respond to the non-approvable letter on 7/1/99.
A teleconference was held on 8/17/99 between FDA and J&J to discuss issues relating to the non-approval.
J&J submitted an amendment to the NDA as response to the non-approvable letter on 1/21/00.

## 2.5. Evolution of Proposed Indication

J&J has proposed different indications at different times for their miconazole nitrate 0.25% ointment drug product:

**Proposed Indications for J&J's Miconazole Nitrate 0.25% Ointment**

| Date | Context | Proposed Indication |
|---|---|---|
| 1/9/97 | Pre-NDA meeting for NDA 21-026 | Treatment of acute diaper rash and the prevention of the onset of severe diaper rash |
| 4/6/98 | Submission to IND | Treatment of moderate and severe diaper dermatitis where *Candida albicans* is suspected |
| 8/24/98 | Original NDA 21-026 | Treatment of moderate to severe diaper dermatitis where *Candida albicans* may be a contributing factor |
| 1/21/00 | Response to non-approvable letter for NDA 21-026 | Infants with diaper dermatitis |

## 3. Clinical Program in Support of NDA 21-026

The clinical program in support of the indication for this NDA consists of 5 phase 1 studies (4 dermal safety studies and one PK study) and 3 phase 3 studies:

**Clinical Studies for PEDIASTAT™ Ointment in the Treatment of Diaper Dermatitis in Infants**

| Study No. | Study Title and Dates | Design | Treatment Arms | Subject No. (M/F) | Age |
|---|---|---|---|---|---|
| Phase 1 | | | | | |
| 83-513T | Photoxicity Test (10/25/83-10/28/83) | phase 1, open-label | | 10 (2/8) | 20-63 |
| 83-513A | Photoallergy Test (10/31/83-12/8/83) | phase 1, open-label | | 31 (2/29) | 20-63 |
| 83-129 | Draize Sensitization Test (12/5/83-1/3/84) | phase 1, open-label | | 216 (60/156) | 18-68 |
| 277.0184 | Cumulative Irritancy Test (1/25/84-2/8/84) | phase 1, open-label | | 26 (1/25) | 18-65 |
| 12966.37C | Absorption and Efficacy of Miconazole Nitrate in Infants with Diaper Dermatitis Associated with Systemic Pathology (7/19/88-6/14/89) | phase 1, open-label uncontrolled non-crossover | MN 0.25% MN 2% | 24 19 5 (12/12) | 1-12 mo (av 7 mo) |
| Phase 3 | | | | | Age in Months |
| 10833/ 10842. 33 | Multicenter Evaluation of BPC Formula No. 610-58 in Treatment of Acute Diaper Dermatitis in Infants (11/7/83-6/23/84) | phase 3, R, DB, PCB, parallel | MN 0.25% OB | 107 53 54 (48/59) | 1.8-12 (av 7.1) |
| 12966.37A | Evaluation of Efficacy of BPC Formula No. 610-73 in Treatment of Acute Diaper Dermatitis in Infants (2/27/89-3/21/90) | phase 3, R, DB, PCB, parallel | MN 0.25% OB | 202 101 101 (107/95) | 1.7-13 (av 5) |
| 12966.37B | Multicenter Evaluation of Efficacy of BPC Formula No. 610-73 in Treatment of Acute Diaper Dermatitis in Infants (12/7/88-11/10/89) | phase 3, R, DB, PCB, parallel | MN 0.25% OB | 196 98 98 (91/105) | 1.7-12 (av 5.8) |

*R=randomized, DB=double-blind, PCB=placebo-controlled, balanced, MN=miconazole nitrate, OB=ointment base

## 4. Efficacy Evaluation

4.1. Dose-ranging

J&J has not conducted dose-ranging studies but chose miconazole nitrate 0.25% arbitrarily, based on their view that this concentration is still over 1000x the upper range of the MIC for *C. albicans*. They state: "This 0.25% miconazole nitrate ointment is not intended as a treatment specifically for candidiasis or candidal infections. Instead, the ability of 0.25% miconazole nitrate to control *Candida albicans* is the mechanism which explains the efficacy of this treatment for diaper dermatitis."

4.2. Phase 3 Program

The phase 3 program was originally to be based on a single-center study, but an additional center was added to constitute two studies for NDA The data have been combined as one study for NDA 21-026 (10833/10842.33). The two Australian studies (12966.37A and .37B) were conducted subsequent to All three phase 3 studies are considered to be adequate and well controlled by the Applicant.

4.2.1. Similarities among the Three Phase 3 Trials

- Objectives: comparative efficacy of J&J's miconazole nitrate 0.25% ointment vs the ointment base in (1) treatment of acute diaper dermatitis in infants and (2) prevention of the onset of severe diaper dermatitis.
- Design: Randomized, double-blind, placebo-controlled, parallel-group studies with 2 arms (miconazole nitrate 0.25%:placebo = 1:1).
- Inclusion: (1) Males or females, (2) aged 2-12 months, and (3) "dermatological manifestations consistent with a diagnosis of diaper dermatitis".
- Exclusion: (1) Sensitivity to miconazole nitrate or ointment base, (2) active dermatological conditions other than diaper rash, (3) allergy or sensitivity to skin care toiletry products or disposable diapers and (4) chronic use of medication (e.g., insulin, antihistamines or corticosteroids).
- Dose and administration: Parents were to apply the test drug sparingly (amount not specified) to the clinically affected area after every diaper change and after bathing, over a 7-day period (even if cleared).
- Evaluation times: Days 0, 1, 3, 5 and 7.

4.2.2. Differences between the Three Phase 3 Trials

**Key Differences in the Protocols of Phase 3 Studies**

| | 10833/10842.33 | 12966.37A | 12966.37B |
|---|---|---|---|
| Enrollment | | | |
| Location | U.S. | Australia | Australia |
| Centers | 2 | 1 | 2 |
| Planned sample size | 100 | 200 | 200 |
| Special enrollment effort[1] | + | - | - |
| Objectives | | | |
| Evaluate efficacy in the prevention of onset of - | severe dd[5] due to *C. albicans* | severe dd | severe dd |
| Assess the role of Candida | - | + | - |
| Product Use | | | |
| Miconazole nitrate formula | 610-58 | 610-73 | 610-73 |
| Disposable wipes | mandatory use of J&J's | no specific brand | no specific brand |
| Cleansing bars | mandatory use of J&J's | no specific brand | no specific brand |
| Evaluation | | | |
| Rash score evaluation[2] | 10 sites | 11 sites | 11 sites |
| Overall rating[3] | compared to baseline | compared to last visit | compared to last visit |
| Global clinical Impression[4] | not evaluated | evaluated | evaluated |
| Microbiology cultures | anal and rash | anal and rash | not collected |
| Adverse experience definition | any unwanted sign/symptom | drug-related only | drug-related only |

[1] To ensure inclusion of a suitable number of infants likely to develop *C. albicans* infection, an effort was made to enroll infants (a) with recurrent acute diaper rash and/or (b) having had a course of systemic antibiotics within 7 days of entry or about to receive one.
[2] 0=none, 1=mild erythema with minimal maceration and/or chafing, 2=moderate erythema with or without satellite papules with maceration and chafing, 3=severe erythema with papulopustules and maceration, and 4=extreme erythema with erosions or ulceration.
[3] 1=cured (no rash), 2=improved, 3=same, 4=worse and 5=recurred.
[4] Also called "overall clinical impression"; 0=none, 1=mild, 2=moderate and 3=severe.
[5] dd=diaper dermatitis

**Sites for Rash Severity Score Evaluation in Phase 3 Studies**

| | 10833/10842.33 (10 sites) | 12966.37A & .37B (11 sites) |
|---|---|---|
| Front | upper body<br>abdomen<br>genital area<br>right and left lower extremities | upper body<br>abdomen<br>genitals<br>right and left inner thighs |
| Back | back<br>lower back<br>buttocks<br>right and left lower extremities | back<br>perianal region<br>right and left buttocks<br>right and left outer thighs |

4.2.3. Study Design of Phase 3 Trials

J&J has not provided a rationale justifying the extrapolation of the Australian trial data to U.S. patients. Evidence attesting to the similarity in medical and parenting practices as well as racial composition would be important in the acceptance of these foreign data (ICH Guidance E5 Document)

Furthermore, the three phase 3 studies had flaws that made them inadequate to provide substantial evidence of effectiveness:

- 10833/10842.33 was not adequately powered.
- 12966.37A was a single-centered trial (single-centered studies are generally not considered adequate).
- 12966.37B did not have microbiological evaluation for an antifungal product.

4.2.3.1. Problems in the Conduct of the Phase 3 Trials

- In all three phase 3 trials, inclusion was based on clinical manifestations consistent with a diagnosis of diaper dermatitis. For a properly defined indication, it should have also been based on microbiological evidence of *C. albicans* infection.

- The subjects were enrolled regardless of disease severity, whereas the indication originally requested was "moderate to severe" diaper dermatitis, based on *post-hoc* analysis (10833/10842.33) or a scale without definition details (12966.37A and .37B) (see Section 4.2.3.2.).

- Allowing the use of antibiotics during the study could be problematic. Patients might be about to start antibiotic on entry (10833/10842.33), or allowed chronic antibiotic therapy (12966.37A and .37B).

- The mandatory use of certain disposable wipes and cleansing bars might impact on the study results and result in restrictions in labeling (10833/10842.33).

4.2.3.2. Problems in Evaluation

- The "total rash score" was a composite of scores from 10 or 11 potential sites, some of which were not covered by diaper. The inclusion of upper body sites not covered by diaper for rash scoring is misleading. Rash at such sites might not be generally regarded as "diaper dermatitis". The extent to which the lower extremities were covered by diaper might have also been minimal.

- The counting of numbers of rashes and scoring might be difficult if a rash covered more than one contiguous location. The severity might have been exaggerated by counting this as more than one rash and thus the scoring doubled or even tripled.

- Overall rating for diaper dermatitis was a comparative endpoint, not given in the protocol but only in the case report forms. In 10833/10842.33, it was a comparison vs baseline. However, in 12966.37A and .37B, it was a comparison vs last visit. As the comparison in these two studies was based on a moving target, these data were generally not interpretable and the only valid grading for this endpoint was "clinically cured".

- The overall (global) clinical impression was a static global evaluation used in 12966.37A and .37B. It was also not given in the protocol, but appeared in the case report forms with no descriptors for the scores "mild", "moderate" or "severe". The only easily interpretable value was "none" for this endpoint. It would be difficult to stratify by disease severity in support of the original proposed indication.

- In 10833/10842.33, there was no entry definition of "moderate" or "severe" diaper dermatitis, and the Applicant arbitrarily distinguished these categories *post-hoc* on the basis of the baseline "total rash score" as follows:

| Total Rash Score | Severity |
|---|---|
| 1- 2 | mild |
| 3- 6 | moderate |
| 7-21 | severe |

Hence, the analysis in support of "moderate to severe diaper dermatitis" in this study was derived entirely from this arbitrary *post-hoc* separation. The "total rash score" has a range of 0-40 rather than an upper limit of 21, and even with exclusion of scores of the upper body, it should range between 0-32. In fact, only patients with the mildest scores (1-2) were regarded as "mild" and everyone else (3-21) regarded as "moderate" or "severe". It would be inappropriate to base stratification by severity on a questionable scale.

- Culture alone might not distinguish between colonization and infection by *C. albicans*. The study should have included KOH examination to look for pseudohyphae as evidence of infection.

- The studies did not define a primary parameter for success. For antifungals, the primary variable is generally taken to be clinical and mycologic clearing (KOH and culture) at the end of treatment and a prespecified time point of follow-up. None of the studies had follow-up evaluation beyond the end of treatment on day 7.

4.3. Results on Efficacy in Phase 3 Studies

The phase 3 trials were used by J&J to support efficacy of their proposed indication "treatment of moderate to severe diaper dermatitis where *Candida albicans* may be a contributing factor" in the original NDA submission in 1998. Normally clinical trials are performed with clear-cut prespecified hypotheses for the demonstration of efficacy. FDA generally discourages *post-hoc* analysis of data in search of an indication. The clinical trials in this NDA were not designed to support an indication based on analysis with multiple stratifications.

The proposed indication in the original NDA was vague, because it did not clearly define usage in relation to *Candida albicans* infection. The term "may be" should have no place in describing an indication. Moreover, the role of *Candida albicans* in the condition to be treated is described as "contributory" but not characterized. J&J postulated that Candida products (cell fragments and released components) might be responsible for symptomatology even in the absence of infection. No data were presented by the Applicant to bolster this assumption in clinical cases of diaper dermatitis with or without *C. albicans* infection.

The following data are extracted from the review by the Biometrics Reviewer, presented using the intent-to-treat (ITT) population with last observation carried forward (LOCF) for the day 7 (end-of-treatment) results.

### 4.3.1. Study 10833/10842.33

**Efficacy Data at End of Treatment (Day 7) for Study 10833/10842.33**

| | Active | Ointment Base | p-value |
|---|---|---|---|
| Complete Data Set | N=53 | N=54 | |
| Patients with rash score=0 | 28 (53%) | 22 (41%) | 0.212 |
| *C. albicans* culture negative | 48 (91%) | 42 (78%) | 0.072 |
| *C. albicans* culture negative and rash score = 0 | 27 (51%) | 21 (39%) | 0.212 |
| Patients with Baseline Positive *C. albicans* Culture | N=17 | N=19 | |
| Patients with rash score=0 | 6 (35%) | 3 (13%) | 0.183 |
| *C. albicans* culture negative | 14 (82%) | 10 (53%) | 0.063 |
| *C. albicans* culture negative and rash score = 0 | 6 (35%) | 3 (13%) | 0.183 |
| Patients with Baseline Negative *C. albicans* Culture | N=36 | N=35 | |
| Patients with rash score=0 | 22 (61%) | 19 (54%) | 0.563 |
| *C. albicans* culture negative | 34 (94%) | 32 (92%) | 0.622 |
| *C. albicans* culture negative and rash score = 0 | 21 (58%) | 18 (51%) | 0.562 |

### 4.3.2. Study 12966.37A

**Efficacy Data at End of Treatment (Day 7) for Study 12966.37A**

| | Active | Ointment Base | p-value |
|---|---|---|---|
| Complete Data Set | N=101 | N=101 | |
| Patients with rash score=0 | 56 (55%) | 22 (30%) | <0.001 |
| *C. albicans* culture negative | 98 (97%) | 42 (57%) | <0.001 |
| *C. albicans* culture negative and rash score = 0 | 55 (55%) | 21 (28%) | <0.001 |
| Patients with Baseline Positive *C. albicans* Culture | N=30 | N=33 | |
| Patients with rash score=0 | 19 (63%) | 0 (0%) | <0.001 |
| *C. albicans* culture negative | 29 (97%) | 3 (9%) | <0.001 |
| *C. albicans* culture negative and rash score = 0 | 19 (63%) | 0 (0%) | <0.001 |
| Patients with Baseline Negative *C. albicans* Culture | N=71 | N=68 | |
| Patients with rash score=0 | 37 (52%) | 30 (44%) | 0.347 |
| *C. albicans* culture negative | 69 (97%) | 55 (81%) | 0.002 |
| *C. albicans* culture negative and rash score = 0 | 36 (51%) | 28 (41%) | 0.262 |

### 4.3.3. Study 12966.37B

**Efficacy Data at End of Treatment (Day 7) for Study 12966.37B**

| | Active | Ointment Base | p-value |
|---|---|---|---|
| Complete Data Set | N=98 | N=98 | |
| Patients with rash score=0 | 60 (61%) | 26 (27%) | <0.001 |
| *C. albicans* culture negative | N/A | N/A | N/A |
| *C. albicans* culture negative and rash score = 0 | N/A | N/A | N/A |

## 4.4. Overview of Efficacy

### 4.4.1. Efficacy for the Indication "Moderate to Severe Diaper Dermatitis where *Candida albicans* May be a Contributing Factor"

#### 4.4.1.1. Study 10833/10842.33

The design of 10833/10842.33 would not have allowed evidence to be established to support "treatment of moderate to severe diaper dermatitis where

*C. albicans* may be a contributing factor", particularly because of (a) inability to define *C. albicans* infection, (b) post-hoc definition of disease severity using a questionable scale, and (c) small sample size.

There were only 32 patients with positive *C. albicans* cultures taken from the rash site at baseline (active 15, ointment base 17), and 49 with negative cultures (active 22, ointment base 27). The analysis stratified by Candida status already failed to show efficacy of the drug product in either group (*C. albicans*$^{+}$ or *C. albicans*$^{-}$) (See Section 4.3.1.) with respect to clinical cure (rash score=0). Further analysis with double stratification by both Candida status and disease severity would be even less likely to demonstrate efficacy, especially with the generally accepted endpoint, clinical plus mycologic cure, which is more stringent. In an amendment submitted on 11/19/98 upon the Agency's request for proper stratification, J&J stated: "The modest sample size does not support multiple stratification by *C. albicans* and severity."

4.4.1.2. Study 12966.37A

The following data were submitted by J&J at the request of FDA for stratification. They show the total rash scores in patients who had moderate or severe diaper dermatitis (by overall clinical impression) at baseline:

**Total Rash Scores in Patients with Moderate or Severe Diaper Dermatitis (Mean±S.D.)**

| | Active | | Ointment Base | | |
|---|---|---|---|---|---|
| | N | Mean±SD | N | Mean±SD | p-value |
| Baseline rash *C. albicans*+ | | | | | |
| day 0 | 22 | 9.2±2.8 | 26 | 9.5±3.5 | 0.763 |
| day 7 | 22 | 2.9±4.4 | 26 | 9.4±5.6 | <0.001 |
| Baseline rash *C. albicans*- | | | | | |
| day 0 | 26 | 8.7±4.0 | 23 | 9.3±2.4 | 0.309 |
| day 7 | 26 | 3.4±4.2 | 23 | 5.4±3.9 | 0.083 |

The data show superiority of active over ointment base in the group with positive baseline *C. albicans* cultures. They do not support use in those cases where baseline *C. albicans* cultures are negative.

Clinical and mycologic cure is the usual criterion for demonstration of efficacy of an antifungal. J&J has not presented a comparison between the treatment groups with respect to the proportion of patients showing clinical clearing and negative culture for *C. albicans* at the end of treatment. This analysis actually shows a rate of 55% (12/22) in the active treatment group and none (0/27) in the ointment base group ($p<0.001$).

These are the data closest to supporting an indication for the treatment of moderate to severe diaper dermatitis where *C. albicans* has been found to be present at the rash site by culture at baseline. However, the data quality is not ideal, because of (a) inability to properly define *C. albicans* infection, and (b) problem with disease severity scale (see Section 4.2.3.2.).

4.4.1.3. Study 12966.37B

As there are no microbiological data in this study, it does not support efficacy of the drug product in the diaper dermatitis strata by *C. albicans* status.

4.4.1.4. Conclusion on Efficacy for the Indication "Moderate to severe Diaper Dermatitis where *Candida albicans* May be a Contributing Factor"

This indication is not supported by 10833/10842.33 or 12966.37B. Study 12966.37A suggests superiority of J&J's miconazole nitrate 0.25% ointment in patients with moderate and severe diaper dermatitis and baseline cultures positive for *C. albicans.*

4.4.2. Efficacy for the Indication "Infants with Diaper Dermatitis"

Although it is not appropriate to either (1) consider diaper dermatitis *per se* as an indication for an antifungal, or (2) search for an indication based on post-hoc viewing of data, J&J has now returned to the original objective of the clinical studies and proposed "infants with diaper dermatitis" as the indication of its miconazole nitrate 0.25% ointment.

The majority of cases of diaper dermatitis do not have *C. albicans* involvement (57% in 10833/10842.33 despite an effort to enroll patients that might have Candida involvement; 69% in 12966.37A). The appropriateness of the use of an antifungal in a condition where there is no fungal involvement, and thus where it is not indicated, is questionable.

Notwithstanding this dilemma and the flaws in the design of the phase 3 studies (see Section 4.4.1.), it is still necessary to evaluate the efficacy of J&J's miconazole nitrate 0.25% ointment in the treatment of "diaper dermatitis", the original objective of the trials. The analysis for patients with or without positive *C. albicans* cultures and for the entire dataset in each study by the Biometrics Reviewer has been shown in Section 4.3.

4.4.2.1. Study 10833/10842.33

This study has not demonstrated efficacy of J&J's miconazole nitrate ointment over the ointment base in terms of clinical cure for the entire dataset (total rash score=0: active 53% and ointment base 41%; p=0.212) or for either subset by Candida status (See Section 4.3.1.). Further analysis also did not demonstrate efficacy using the criterion clinical cure plus negative mycologic culture. This study was the basis of

4.4.2.2. Study 12966.37A

This is a single-center study, which is not generally considered adequate to demonstrate efficacy. J&J's miconazole nitrate 0.25% ointment was superior to its ointment base for clinical cure after 7 days of treatment for the entire dataset (total rash score=0: active 55% and ointment base 30%; p<0.001) and the subset with positive Candida cultures (total rash score=0: active 63% and ointment base 0%; p<0.001) (See Section 4.3.2.), but not that with negative cultures. Further

analyses using the criterion clinical cure plus negative mycologic culture gave results consistent with those on clinical cure. As this study did not provide for a follow-up evaluation, there is no information on relapse.

4.4.2.3. Study 12966.37B

Although J&J's miconazole nitrate 0.25% ointment was superior to its ointment base for clinical cure after 7 days of treatment (total rash score=0: active 61% and ointment base 27%; p=0.001) (See Section 4.3.3.), the study is not considered adequate for an antifungal product. It did not collect mycologic data or provide for a follow-up evaluation, Demonstration of clinical cure alone without mycologic data would be inadequate to support efficacy for an antifungal.

4.4.2.4. Conclusion on Efficacy for the Indication "Infants with Diaper Dermatitis"

Although 12966.37A and 12966.37B provide an efficacy signal in otherwise not characterized "diaper dermatitis", both the indication and the studies are inadequate. Importantly, efficacy of miconazole nitrate 0.25% in the majority subset (with negative *C. albicans* culture; 57% to 69% in the two studies with mycologic data) has not been demonstrated. Efficacy of this antifungal in the minority subset (with positive C. albicans culture) is suggested in one study (12966.37A). Additional adequate and well designed studies would be needed to support a well defined indication that describes a clinically useful characterization of diaper dermatitis subset(s).

4.4.3. Efficacy of J&J's Miconazole Nitrate 0.25% Ointment in Diaper Dermatitis of Elderly, Hospitalized Patients

A study for safety and efficacy in diaper dermatitis has been conducted in elderly, hospitalized patients. J&J has included this study in the original NDA submission for safety data.

The study, "Miconazole in a Zinc Oxide Base in the Treatment of Diaper Dermatitis in Geriatric Patients (Protocol MIC-BEL-1)", was a single-center, randomized, placebo-controlled, parallel-group trial conducted in Belgium, comparing J&J's miconazole nitrate 0.25% ointment with the ointment base (miconazole:ointment base=38:40 patients) in elderly, hospitalized patients having diaper dermatitis, with double-blind treatment for 14 days. Superiority of the miconazole nitrate 0.25% ointment was not demonstrated. One patient developed "moniliasis genitalis".

5. Safety Evaluation

The safety database for J&J's miconazole nitrate 0.25% ointment has been derived from 5 phase 1 studies (4 dermal safety studies and one PK study) and 3 phase 3 studies (see Table in Section 3). In addition, the drug product was used in a study for the treatment of perineal dermatitis in hospitalized, elderly patients involving 78 subjects.

5.1. Dataset/Exposure Information

The original proposed indication in this NDA was for "moderate to severe diaper dermatitis where Candida albicans may be a contributing factor". The dataset in support of intended use has been primarily derived from the phase 3 trials, where the to-be-marketed product or ointment base was applied to the lesions to be treated at every diaper change or after bathing in the target population for 7 days. However, there was no microbiologic evaluation in 12966.37B to allow analysis by stratification. As the two Australian studies,12966.37A and 12966.37B, had the same basic design, one may estimate by extrapolation (from 12966.37A) the strata in 12966.37B. The following Tables show the patient numbers exposed to the study medications and the estimated strata:

**Patient Exposure to J&J's Miconazole Nitrate 0.25% Ointment or Ointment Base in Phase 3**

| | Active | | | Ointment Base | | | Grand |
|---|---|---|---|---|---|---|---|
| | Mild | Mod/Severe | Total | Mild | Mod/Severe | Total | Total |
| 10833/108432.33 | 14 | 39 | 53 | 10 | 44 | 54 | **107** |
| 12966.37A | 53 | 48 | 101 | 52 | 49 | 101 | **202** |
| 12966.37B | 48 | 50 | 98 | 47 | 51 | 98 | **196** |
| Total | 115 | 137 | 252 | 109 | 144 | 253 | **505** |

**Patient Numbers for Subsets by Positive Rash Site Culture for *C. albicans* at Baseline**

| | Active | | | Ointment Base | | | Grand |
|---|---|---|---|---|---|---|---|
| | Mild | Mod/Severe | Total | Mild | Mod/Severe | Total | Total |
| *C. albicans+* | | | | | | | |
| 10833/108432.33 | 2 | 15 | 17 | 2 | 17 | 19 | **36** |
| 12966.37A | 8 | 22* | 30* | 8 | 27 | 35 | **65*** |
| Total | 10 | 37 | 47 | 10 | 44 | 54 | **101** |
| *C. albicans-* | | | | | | | |
| 10833/108432.33 | 12 | 22 | 34 | 8 | 27 | 35 | **69** |
| 12966.37A | 45 | 26* | 71* | 44 | 22 | 66 | **137*** |
| Total | 57 | 48 | 105 | 52 | 49 | 101 | **206** |

*not including two patients without culture data.

**Estimated Patient Numbers for Subsets by Positive Rash Site Culture for *C. albicans* at Baseline**

| | Active | | | Ointment Base | | | Grand |
|---|---|---|---|---|---|---|---|
| | Mild | Mod/Severe | Total | Mild | Mod/Severe | Total | Total |
| *C. albicans+* | | | | | | | |
| 10833/108432.33 | 2 | 15 | 17 | 2 | 17 | 19 | **36** |
| 12966.37A | 8 | 22* | 30* | 8 | 27 | 35 | **65*** |
| 12966.37B (estimated) | 7 | 23 | 30 | 7 | 28 | 35 | **65** |
| Total (estimated) | 17 | 60 | 77 | 17 | 72 | 89 | **166** |
| *C. albicans-* | | | | | | | |
| 10833/108432.33 | 12 | 22 | 34 | 8 | 27 | 35 | **69** |
| 12966.37A | 45 | 26* | 71* | 44 | 22 | 66 | **137*** |
| 12966.37B (estimated) | 41 | 27 | 68 | 40 | 23 | 63 | **131** |
| Total (estimated) | 98 | 75 | 173 | 92 | 72 | 164 | **337** |

*not including two patients without culture data.

Although there were 252 patients who were treated with J&J's miconazole nitrate 0.25% ointment in the phase 3 studies, the number of patients who had positive baseline *C. albicans* cultures at rash sites and treated with this drug product is estimated to be only 77. Similarly, only an estimated 89 out of 253 patients treated with ointment base had *C. albicans* cultured from the lesions at baseline.

Approximately two-thirds of the patients in phase 3 studies did not have *C. albicans* cultured from the lesions. Further stratification shows that among those who had positive baseline *C. albicans* culture and had "moderate" and "severe" disease (original proposed indication), the estimated number of patients who used miconazole nitrate 0.25% ointment was 60 (ointment base 72).

5.2. Adverse Event Data

The Australian studies 12966.37A and 37B defined adverse experiences as "any unwanted signs or symptoms which may in any way be related to the drug." The study reports included "unrelated" concomitant illnesses in the adverse event profile.

5.2.1. Significant/Potentially Significant Adverse Experiences

Deaths: No deaths were reported in the trials for diaper dermatitis in infants.

Serious Adverse Events: Out of the 505 subjects in phase 3 studies, there were no reported serious adverse events.

Discontinuations due to Adverse Events: Two patients discontinued due to adverse events in the phase 3 trials. Both were on the ointment base. The events were: gastroenteritis in one, and rash with swelling of hands and feet in the other.

5.2.2. Adverse Event Table

There were relatively few adverse experiences reported in the phase 3 trials. There were more adverse events in the ointment base-treated group in each trial. However, these events generally occurred outside the area of drug application and relationship to the use of test medication was uncertain.

**Combined Adverse Event Data from Phase 3 Studies**

| | Active (N=252) | Ointment Base (N=253) |
|---|---|---|
| Total Number of Subjects with AE | 23 | 54 |
| Body as a whole | | |
| Fever | 2 | 4 |
| routine vaccination | 0 | 1 |
| reaction from DPT vaccine | 1 | 0 |
| Cardiovascular | | |
| 4th heart sound audible | 0 | 1 |
| ENT | | |
| cold | 3 | 2 |
| croup | 0 | 1 |
| nasal congestion | 1 | 0 |
| oral thrush | 1 | 5 |
| otitis externa | 0 | 1 |
| otitis media | 2 | 5 |
| rhinitis | 1 | 0 |
| rhinorrhea | 1 | 2 |
| tonsillitis | 0 | 1 |
| tonsillitis/croup | 1 | 0 |
| URI | 2 | 18 |
| Eye | | |
| conjunctivits | 3 | 1 |
| Gastrointestinal | | |
| diarrhea | 2 | 5 |
| gastric disorder | 0 | 1 |
| gastroenteritis | 0 | 1 |
| vomiting | 1 | 2 |
| Musculoskeletal | | |
| inguinal hernia | 0 | 1 |
| Nervous | | |
| irritability | 0 | 1 |
| hypotonia | 1 | 0 |
| Respiratory | | |
| Asthma | 0 | 1 |
| bronchiolitis | 0 | 1 |
| bronchitis | 1 | 2 |
| Skin and appendages | | |
| abscess of right thigh | 1 | 0 |
| erythema multiforme | 0 | 1 |
| rash | 1 | 3 |
| seborrheic dermatitis | 0 | 2 |
| Total adverse experiences | 25 | 63 |

There were only three "drug-related" adverse experiences: 2 cases of rash (1 in active and 1 in ointment base group), and 1 case of erythema multiforme (ointment base).

5.3. Dermal Safety Studies

Four dermal safety studies were conducted for J&J's miconazole nitrate 0.25% ointment using standard methodology in the early 1980s on healthy adult subjects (See Table in Section 3). Evidence for irritancy, contact sensitization potential, phototoxicity, and photoallergenicity was not observed.

The dermal safety studies were performed in adults and not in infants. They were done on the back or the forearms, rather than in the diaper area. Caution must also be exercised in the extrapolation of their data.

In these studies, a previous version of miconazole nitrate 0.25% ointment, used in the first phase 3 study (10833/10842.33), was tested. The difference between this formulation and the newer one proposed for marketing (used in the two other phase 3 studies, 12966.37A and .37B, and the pharmacokinetic study, 12966.37C) lies in the
(older vs newer formulation). Both are of the same concentration in the formulation. The newer formulation only deleted one component , and is not expected to increase the dermal toxicity of the product.

5.4. Pharmacokinetics Study

A PK study (Protocol 12966.37C) was conducted in Mexico as an uncontrolled, open-label, non-crossover trial in infants (aged 1-12 months) hospitalized for systemic conditions, primarily gastroenteritis. Test medication (current formulation of miconazole nitrate 0.25% ointment or 2% cream) was applied to the affected area at each diaper change for 7 days. Day 7 blood concentrations of miconazole were found to be <1 ng/mL in 15/19, and 1-5 ng/mL in 3/19 infants treated with miconazole nitrate 0.25% ointment (current formulation). One subject's samples were missing. The blood concentrations in the 4/5 infants treated with 2% miconazole nitrate cream ranged between 5.2-7.4 ng/mL and was <1 ng/mL in one. No adverse events developed in the study.

Infants in hospital may receive more attention and nursing care. Those hospitalized with gastroenteritis may have more frequent cleansing and diaper changes than outpatients. This potentially increases drug exposure, as application is associated with each diaper change. Despite this, the majority of patients who received miconazole nitrate 0.25% ointment showed undetectable blood levels, and the remainder achieved concentrations of <5 ng/mL. Therefore, the use of 0.25% miconazole nitrate ointment in diaper rash may be considered to be associated with minimal absorption of miconazole.

The only systemic toxicity shown in preclinical studies with miconazole (in Wistar rats after administration for 78 weeks) was in the liver: centrilobular cloudy swelling, and/or fatty changes with vacuoles and occasionally hyaline degeneration of some hepatocytes. These changes were achieved at oral doses (83-141 mg/kg/d) one log higher than that used topically with the current formulation for diaper dermatitis.

5.5. Potential Adverse Effects of Ointment Base

There are two potential safety concerns with respect to the drug vehicle. An ointment base may cause occlusion that can aggravate the effects of irritants in the diaper area. In addition, the vehicle may contain material that serves as

medium for the growth of microbes, including Candida. At the pre-NDA meeting of 1/9/97, J&J had been advised of FDA's concern and possible approach to resolve it. No new data were presented in the original NDA to address this.

- The improvement in rash scores in diaper dermatitis without *C. albicans* involvement treated with ointment base, as well as clearing in half or more of this group, suggest that an occlusive effect from the ointment base probably did not produce a detectable adverse phenomenon in patients without *C. albicans* involvement.

- In the absence of comparison with a valid control group, an adverse effect cannot be completely excluded, especially in the group with *C. albicans* involvement.

6. Resistance

At the pre-NDA meeting of 1/9/97, J&J was advised to address the issue of resistance. Item 8 of the minutes states: "Questions of microbial resistance need to be resolved."

There were no data presented to address the issue of antimicrobial resistance. Indiscriminate use of this product, particularly in cases that do not involve fungal infection (57 to 69% in the phase 3 trials), may carry a risk for development of resistance by *C. albicans* and other currently susceptible organisms in the long term, such that this antifungal may be rendered ineffective in cases of real need. This is of considerable public health concern. It is particularly disconcerting when the drug product contains miconazole nitrate at a substantially lower than currently available concentration (by a factor of 8) and the target population (infants) has a relatively immature immune system. Thus, it would be of questionable appropriateness to consider this antifungal product for "diaper dermatitis" as an indication, unless it is restricted to those cases where *C. albicans* infection is demonstrated.

In addition, the issue of cross-resistance among azole antifungals has not been addressed. Since the azole antifungals currently used to treat life-threatening infections, fluconazole and itraconazole, act through the same mechanism as the topical antifungals in their fungistatic effect, it is imperative that J&J's low concentration miconazole nitrate ointment (0.25%) does not pose a significant risk in the promotion of drug resistance to the systemic antifungals.

7. J&J Responses to Issues in Non-Approvable Letter of 6/28/99

7.1. Demonstration of Efficacy for J&J's Miconazole Nitrate 0.25% Ointment

J&J provided no new data to support the original indication "diaper dermatitis where *Candida albicans* may be a contributing factor". Instead, the following lines of argument were presented:

- *C. albicans* may contribute to diaper dermatitis even in the absence of infection.
- Many physicians do not depend on demonstration of *C. albicans* infection to prescribe treatment for diaper dermatitis.
- *C. albicans* resistance to miconazole has not emerged as a clinical problem. J&J's miconazole nitrate 0.25% ointment would have a negligible effect on the selection of resistant *C. albicans*.

In conclusion, J&J proposes the following new indication: "infants with diaper dermatitis".

*This response is inadequate because:*

1. *J&J assumes from the literature that cell free material from C. albicans may have an irritancy effect without showing the relevance of this finding in diaper dermatitis. Symptomatology due to the amount of such material exposed to the diaper area appears to be unlikely in the absence of actual infection.*
2. *J&J surveyed pediatricians on the choice of therapy when there was a strong enough suspicion of fungal infection to warrant laboratory tests, and concluded that physicians would often treat diaper dermatitis regardless of lab data. This is an extrapolation from a specific context to a general conclusion. In fact, most diaper dermatitis cases have no fungal element and are cared for by parents or non-physician health care providers.*
3. *J&J has not addressed the potential of resistance in the use of (a) miconazole nitrate at a substantially lower concentration than that currently marketed in (b) infants who have a more immature immune system.*
4. *J&J is requesting a broader indication, when their studies have not demonstrated efficacy even in a narrower indication.*

7.2. Target Population in Future Studies

- J&J provided subset analysis by sex in Study 12966.37A for the group of patients with positive baseline *C. albicans* culture.
- There is an absence of comments in the labels of other miconazole products or products for diaper rash with respect to age, race or gender.

*The response is inadequate because J&J has not presented a proposal for new studies. This issue on inclusive enrollment with respect to race and sex is intended to be advice for future studies. The phase 3 trials with evaluable data on ethnicity included only 4 non-Caucasians.*

7.3. Potential Adverse Effect of Ointment Base

- J&J agrees that the possibility of adverse effect from the ointment base cannot be excluded based on available data. However, this is unlikely because of (1) the improvement in patients with negative Candida cultures,

(2) data from dermal safety studies, and (3) the ointment base consistent with conditions specified under the Skin Protectant Tentative Final Monograph.

- There is no appropriate treatment population that may be used as comparison to determine adverse effect from the ointment base.

*J&J has raised some valid problems concerning the investigation of potential adverse vehicle effects. How far this issue should be pursued depends on the anticipated yield of a feasible study. The ideal setting is one comparing vehicle vs no vehicle, both in the presence of standard care. If this is not acceptable to IRBs and parents, there may not be sufficient useful information to be gained by other comparisons.*

8. Summary of Risks and Benefits

It is difficult to address risk/benefit assessment without the context of a specific indication. The proposed indication has changed a number of times. Diaper dermatitis can be considered to consist of at least two indications: irritant dermatitis and irritant dermatitis with secondary fungal infection.

Currently marketed OTC products are under the Proposed Rule of 1990 on diaper rash products for the Skin Protectant Monograph. These are skin protectant products that help to prevent or treat the irritant aspect of diaper dermatitis, and do not address the microbiology of this condition. They may provide modest benefits but are generally regarded as safe and of low risk in cases without fungal infection.

For an antifungal prescription product, the following issues are important in risk/benefit assessment and have been discussed between J&J and FDA at the pre-NDA meeting:

<u>For diaper dermatitis without Candida involvement -</u>

- evidence that the vehicle is not having a negative effect, thus giving a false impression of effectiveness of the active antifungal
- evidence that using an antimicrobial in the absence of infection would not give rise to resistant organisms

<u>For diaper dermatitis with Candida involvement -</u>

- demonstration of colonization vs. infection

For J&J's miconazole nitrate 0.25% ointment, the following assessment pertains:

<u>Benefits:</u>

- Although the antifungal, miconazole nitrate at 0.25% concentration, may be efficacious in the treatment of the fungal component present in a <u>*minority*</u> of cases of diaper dermatitis, the evidence based on the phase 3 studies is inadequate to establish efficacy in this group. Only one <u>*single-center study*</u> (12966.37A) suggested superiority of the product over vehicle ointment in patients with positive *C. albicans* culture at rash site at the end of treatment, but

without follow-up. In none of the studies was superiority shown in the *majority* group, i.e., patients with negative culture at rash site. Therefore, the benefits of J&J's miconazole nitrate 0.25% ointment have not been established.

Risks:

- Resistance development from indiscriminate use of this lower concentration preparation in infants whose immune system may be immature
- Potential for prolonged use in a recurring condition with reservoir for re-infection and primary cause (occlusion) not removed
- Potential adverse effect of vehicle not excluded

J&J's miconazole nitrate has not been recommended for approval because the benefits have not been established and therefore are outweighed by risks.

9. Questions for Discussion

9.1. "Diaper dermatitis" may be an inadequate statement for an indication for an antifungal. If this term *per se* is not appropriate, what are the subtypes of diaper dermatitis patients that may be studied to obtain an indication?

9.2. Although the use of an antifungal in cases without fungal infection may be problematic, should one still consider it a benefit, e.g., antiinflammatory effect, if it can be demonstrated in this subtype of diaper dermatitis?

9.3. To what extent should an adverse effect of the ointment base on *C. albicans* infection be sought? Please discuss the kind of study design to achieve this, if additional studies are deemed necessary.

9.4. Is the development of resistance by *C. albicans* a serious consideration for J&J's 0.25% ointment in infants with diaper dermatitis in terms of (a) relapse, and (b) public health concern?

9.5. Are the studies done in Australia applicable to U.S. patients?