Introduction

Overview

Recognizing that members of the Advisory Committee may wish to focus on different topics, this document is organized into the following sections to make it easier for readers to locate the information they desire most:

- A bulleted Summary of the major messages derived from the New Drug Application
- Background information presenting a definition of diaper dermatitis; etiologic factors with a focus on the role of *Candida albicans*, clinical and laboratory criteria for diagnosis
- Information about the drug product:
  - Proposed indication
  - Description and dosing
- Efficacy demonstrated in clinical trials
- Safety assessment based on testing for tolerability in volunteers, on experience with use in clinical trials and the very low systemic exposure after topical administration.
- The marketing history in other countries.
- Microbiologic aspects, including the mechanism of action and activity of miconazole against *Candida albicans* and the rarity of reports of *Candida albicans* developing resistance to miconazole.
- Perspective on clinical practice for the diagnosis and treatment of diaper dermatitis.
- Appendices with supporting information for use by committee members as desired.

Summary

PEDIASTAT™ (miconazole nitrate, USP 0.25%) Diaper Rash Ointment is proposed as a prescription drug, indicated for the treatment of diaper dermatitis in infants. It is an ointment intended for topical use containing the synthetic antifungal agent miconazole nitrate (0.25%) in a base containing White Petrolatum, USP and Zinc Oxide, USP.

This formula has been marketed and safely used for the treatment of diaper dermatitis in six (6) countries outside the U.S. since the early 1990s under the trade name DAKTOZIN®.

PEDIASTAT™ is effective.

- PEDIASTAT™ was clinically and statistically superior to the ointment base for diaper dermatitis in infants.
- PEDIASTAT™ demonstrated the greatest advantage over the ointment base in the subgroup of patients who had baseline cultures that were positive for *Candida albicans*.

- PEDIASTAT™ and the ointment base both produced improvement in patients who had baseline cultures that were negative for *Candida albicans*; improvement in this subpopulation was statistically significant for both formulations.
- The ointment base contains concentrations of petrolatum and zinc oxide that would qualify as an OTC drug product for diaper dermatitis under the FDA's Tentative Final Skin Protectant Monograph. However, in these trials the ointment base did not produce clinically or statistically significant improvement for the subset of patients whose baseline cultures were positive for *Candida albicans*.

PEDIASTAT™ is safe.

- Tests in volunteers demonstrated little or no irritant, allergic, phototoxic or photoallergic potential.
- No clinically significant adverse experiences were reported in the clinical trials.
- The only adverse experiences judged by investigators to be related to treatment occurred in the skin and resolved without sequelae. The incidence of these reactions was less than 1% for both the PEDIASTAT™ and ointment base treatment groups.
- Adverse experiences occurred half as often with PEDIASTAT™ as with the ointment base. Investigators judged these reactions to be coincidental illnesses that were unrelated to treatment.

PEDIASTAT™ is a valuable treatment option.

- There are currently no prescription medications with a diaper dermatitis indication.
- There are currently no topical antifungal products approved for treatment of children younger than three years.
- PEDIASTAT ™ produced an overall benefit compared to the ointment base.
- PEDIASTAT™ proved superior in patients with baseline cultures that were positive for *Candida albicans*, whereas the ointment base alone was not effective.
- PEDIASTAT™ would provide an alternative to combination products containing a corticosteroid and an antifungal because it offers the barrier protection of zinc oxide and petrolatum with antifungal activity to reduce or control *Candida albicans*.

PEDIASTAT™ is not likely to lead to the development of miconazole-nitrate-resistant *Candida*.

Miconazole is widely used in prescription and non-prescription products, including extensive use for vaginal yeast infections. In addition to medical use, azole molecules are widely used in agriculture. Despite extensive use, this experience indicates that reports of true resistance to miconazole are rare.

Background

Definition of diaper dermatitis

Diaper dermatitis is defined by the clinical features of irritant dermatitis developing in the area covered by diapers. It is the most common skin disorder in infancy (Hurwitz, 1993). This disorder is estimated to affect 7-50% of infants between 2 and 18 months of age (Benjamin, 1987). Diaper dermatitis also appears to be related to an infant's age and is more common in older infants (>6 months).

Physical examination of diaper dermatitis consistently shows erythema and, depending on the severity, varying degree of edema, erosions (or vesicles) or both. Finding papules or pustules (referred to as satellite lesions) surrounding or within the main area suggests the presence of *Candida albicans* but such findings are not pathognomonic.

Etiologic Factors

There is general agreement that diaper dermatitis is a multi-factorial, irritant dermatitis. Commonly cited contributory factors include:

- Physical consequences of wearing diapers (e.g. chafing, friction, occlusion, and a sensitivity to residues of laundry detergents)
- Increased moisture content of skin (especially when the skin is macerated)
- Contact with urine and feces, particularly during bouts of diarrhea or when changes in the diet occur
- *Candida albicans:*
  - Can be demonstrated in many, but not all, patients with diaper dermatitis
  - Can be part of the fecal flora and is a typical isolate of patients with oral candidiasis (thrush)
  - Need not be invasive or even viable to contribute to diaper dermatitis. Either cellular fragments or supernatant from disrupted *Candida* can, under occlusion, produce irritant dermatitis in normal volunteers
- Treatment with oral antibiotics
- Bacteria
- Skin disease active in the diaper area (e.g. atopic dermatitis or seborrheic dermatitis)

Typically several factors are involved simultaneously, but not all have to be present for diaper dermatitis to develop. Proteases and lipases in feces clearly can cause irritation, increase the permeability of skin, and increase potential susceptibility to other factors. (Buckingham, 1986) Urine can contribute to this process by providing urea, which increases

local pH in the presence of fecal urease activity; the higher pH potentiates the activity of fecal proteases and lipases. (Berg, 1986)

Authors who discuss the etiology of diaper dermatitis recognize that *Candida albicans* is commonly part of the fecal flora and is regularly introduced into the diaper area. Some investigators have concluded that the role of *Candida albicans* is that of secondary invader of dermatitic skin, aggravating an underlying process.(Dixon,1969) (Warin,1961) Others suggest that *Candida albicans* plays an important role as a primary causative factor in diaper dermatitis.(Ferguson,1966) (Leyden,1986) (Rippon,1988)

Rebora *et al* stated that it "has not been established that conversion to the filamentous form is always characteristic of or is an obligatory requirement in monilial intertrigo of the skin, though, of course, filamentous forms can sometimes be seen." They performed an experiment in volunteers where they applied *Candida albicans* from a culture broth and covered the inoculum with an occlusive dressing for 24 hours(Rebora,1973). Over the two days after they removed the dressing, they observed a progression from erythema, to small papules, to discrete pustules, reproducing clinical features typical of a *Candida* infection. Increasing the inoculum or maintaining occlusion for longer periods or stripping the stratum corneum with cellophane tape before inoculation increased the incidence and/or severity of clinical reaction. Using less occlusive materials elicited less of a reaction.

A study by Maibach and Kligman demonstrated that invasive infection, as indicated by presence of pseudohyphae, would not be required for *Candida* to contribute to the pathogenesis of diaper dermatitis. They prepared soluble, lyophilized cell-free extract and sterile sediment of ground and ruptured cells from cultures of *Candida albicans*.(Maibach,1962) "Both materials produced a dermatitis in about three-fourths of 30 subjects... The pustular reaction was a reproduction of the disease in miniature, which mimicked in every detail grossly and histologically the features of cutaneous moniliasis. This demonstrated clearly that the living organisms do not have to invade the tissue to produce changes and that toxic substances released by the growth of the organism on the surface are entirely sufficient to evoke the inflammatory response."

These experiments make two important points. First, *Candida albicans* introduced by the fecal flora can become invasive. A negative wet mount for potassium hydroxide examination (KOH) taken when the patient presents does not exclude *Candida albicans* from contributing to or prolonging the episode, because the progression from flora to invasive infection could happen after an infant's first evaluation for diaper dermatitis. Second, *Candida albicans* can irritate skin without being invasive or even viable.

Diagnostic Criteria

Clinical Practice

Diagnosis of diaper dermatitis is commonly made on clinical grounds without laboratory testing. Many physicians find history and physical findings are adequate. Indeed, it is not uncommon for physicians to recommend treatment even when the consultation is made by telephone and the patient is not available for examination or laboratory evaluation.

Laboratory Tests

When the infant is taken to the clinician, it is possible to perform a KOH. Results are available and can influence initial treatment. The presence of pseudohyphae is generally accepted as an indication of active infection, rather than incidental presence. Budding yeasts establish the presence of *Candida* but do not prove active infection. KOHs were not done in any of the studies to support the application, so it is not possible to stratify treatment groups by presence or absence of pseudohyphae.

Cultures can also document the presence of *C. albicans* but they require a minimum of several days to provide results. Consequently treatment must be decided before results are available. Cultures were used in two (2) of the studies to support this application.