Efficacy

Overview of clinical program

Three (3) pivotal studies establish efficacy and safety of 0.25% miconazole nitrate ointment for treatment of acute diaper dermatitis in infants.[1] Studies Australia-A and Australia-B used identical and clinical evaluations, permitting the results to be pooled. Study USA used similar, but not identical, clinical measurements.

Study Design

All three studies were placebo-controlled, randomized, double-blind, parallel-group trials. Subjects in Studies Australia-A and Australia-B, were stratified by the clinical severity of the diaper dermatitis before being randomly assigned to one of two treatment regimens. In Study USA, subjects were randomized but not stratified. In all studies, subjects were treated at each diaper change with either 0.25% miconazole nitrate ointment or the ointment base for a period of seven days. Clinical evaluations of the acute diaper dermatitis were performed pretreatment (Study Day 0), during treatment (Study Days 1, 3, and 5), and on the last day of therapy (Study Day 7).

Microbiological determinations for the presence or absence of *Candida albicans* were performed at baseline and on the last day of therapy in Study USA and Study Australia-A, but not the Australia B

Subject Selection

All three well-controlled studies required that patients be 8 weeks to 13 months of age with diaper dermatitis based on clinical diagnosis. Investigators were able to select "tidemark dermatitis" or candidiasis as an additional clinical assessment when they considered the clinical picture to be candidiasis in the USA Study. Subjects were excluded if they used medications that could influence outcome.

Efficacy Criteria

All three well-controlled studies used investigator evaluations to assess clinical efficacy. Specific sites and total rash score (computed), and overall ratings were performed on Study Days 0, 1, 3, 5, and 7. Studies Australia-A and Australia-B, also included a global clinical impression (none, mild, moderate or severe) by the investigator to evaluate efficacy.

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[1] Australia-A (Protocol 12966.37A), Australia-B (Protocol 12966.37B) and USA (10833/10842.33).

Evaluation of Rash Site

In each study, the investigators evaluated specific sites for the presence of acute diaper dermatitis. In Study USA, ten sites were evaluated. When Studies Australia-A and Australia-B were designed, the sites assessed eliminated the back and added the perianal region and separate ratings for each buttock. Severity of diaper dermatitis was evaluated using the following categorical scale:

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
4 = Extreme erythema with erosions or ulceration

Rash scores at all sites were added together to derive a total rash score for each subject at each day of evaluation (Day 0, 1, 3, 5 and 7). The total rash score was the primary measure of efficacy used in these studies. The maximum total rash score was 40 for Study USA and 44 for Studies Australia-A&B.

Overall Rating

The investigator assigned an overall rating of each subject's clinical response on Study Days 1, 3, 5, and 7, using the following categories:

1 = Cured 2 = Improved 3 = Unchanged 4 = Worse 5 = Recurred

Study USA, compared the clinical response to Day 0 (baseline). Studies Australia-A&B, compared the clinical response to the previous clinical observation.

Global Clinical Impression

In studies Australia-A&B, the investigator assigned a global clinical impression of the subject's rash on Study Days 0, 1, 3, 5, and 7 using the following scale:

0 = None 1 = Mild 2 = Moderate 3 = Severe

The global clinical impression was used to stratify subjects in the studies Australia-A&B, before they were randomized to double-blinded treatment. A rating of the global clinical impression was not performed in study USA.

Microbiological Evaluations

Study USA and Study Australia-A used cultures for yeasts to evaluate the prevalence of *Candida albicans* in diaper dermatitis and the influence of *Candida albicans* on the severity of diaper dermatitis. Anal and rash cultures were collected from each subject before treatment was initiated and at the end of treatment. The pretreatment rash site culture was obtained from the periphery of the inflamed rash, particularly from papulopustules, erosion or ulceration, using a moistened culturette swab. The end-of-

treatment rash culture was taken from the periphery of any residual or recurrent rash. Anal cultures were taken from the external anal mucosa.

Populations for Analysis and Criteria used for Statistical Significance: The level of significance for each test of hypothesis was $p<0.05$ (two-tailed) for all studies. Efficacy analyses were done for intent-to-treat subjects and evaluable subjects. Intent-to-treat analyses included data from all subjects and consisted of 97% of patients admitted to the protocol. Results of the intent-to-treat and evaluable subjects analyses were similar.

Demographics

A total of 505 infants with diaper dermatitis were enrolled into three Phase III trials: 96% of 252 subjects in the PEDIASTAT™ group completed therapy, compared to 90% of 253 subjects in the ointment base group. The mean age was 6 months (range 2 to 13 months); 51% of patients were girls and 64% had a history of diaper dermatitis. There were no significant differences at baseline between the PEDIASTAT™ and the ointment base groups in any of the studies with respect to sex, age, severity of diaper rash at baseline, and history of diaper dermatitis. (Table 1 in Appendix A shows data)

Efficacy Results by Protocol

PEDIASTAT™ was more effective than the ointment base in reducing the total rash scores in all three well-controlled studies. PEDIASTAT™ produced lower total rash scores than patients treated with the ointment base in Study Australia-A (Figure 1A) and Study Australia-B (Figure 1B). Differences between treatment groups were statistically significant on Study Day 5 and 7. Pooling the data for these two studies showed that PEDIASTAT™ was superior to the ointment base and the difference between treatment groups was statistically significant on Study Days 3, 5, and 7 (Table 1 in Appendix A).

FIGURE 1A. MEAN TOTAL RASH SCORES FROM STUDY AUSTRALIA-A: (100 INFANTS PER GROUP)

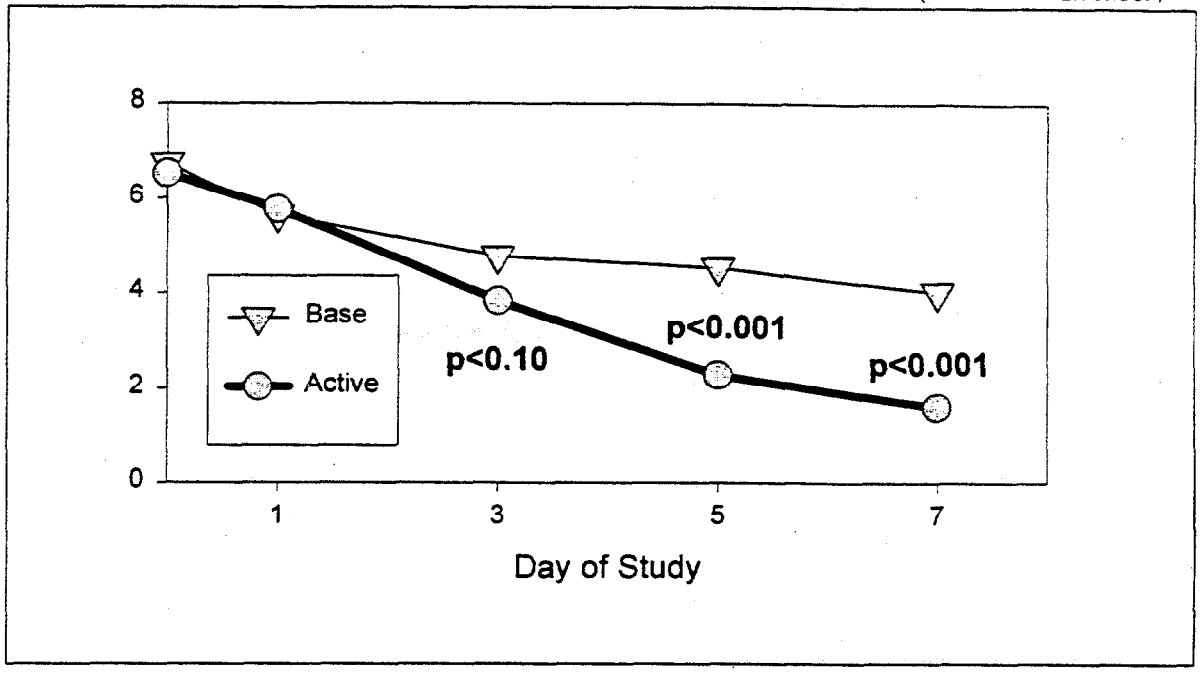
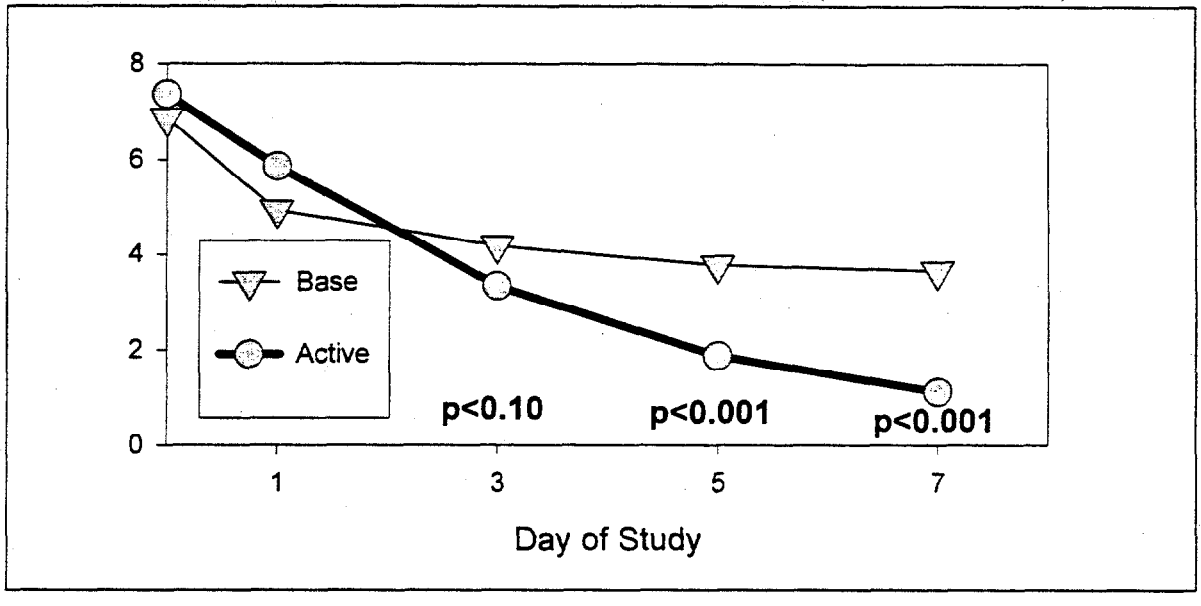
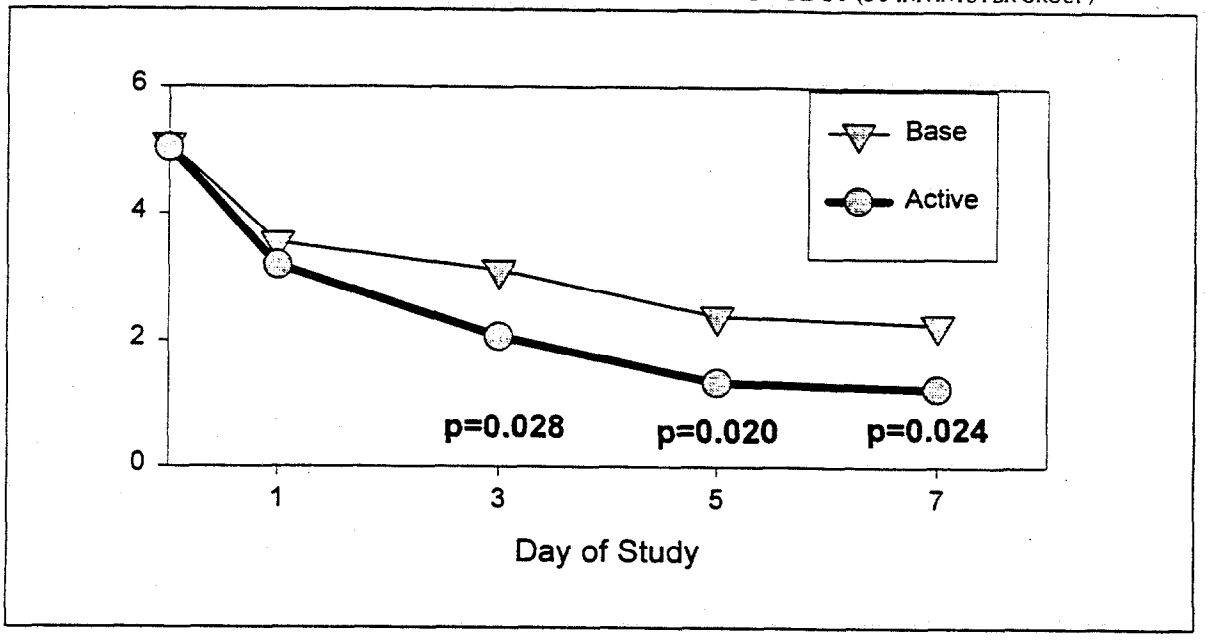


FIGURE 1B. MEAN TOTAL RASH SCORES FROM STUDY AUSTRALIA-B: (~94 INFANTS PER GROUP)



In Study USA, PEDIASTAT™ produced lower total rash scores among evaluable subjects than patients treated with the ointment base. The difference between treatment groups was statistically significant on Study Days 3, 5 and 7 (Figure 1C and Table 1 in Appendix A).

FIGURE 1C. MEAN TOTAL RASH SCORES FROM USA STUDY: (50 INFANTS PER GROUP)

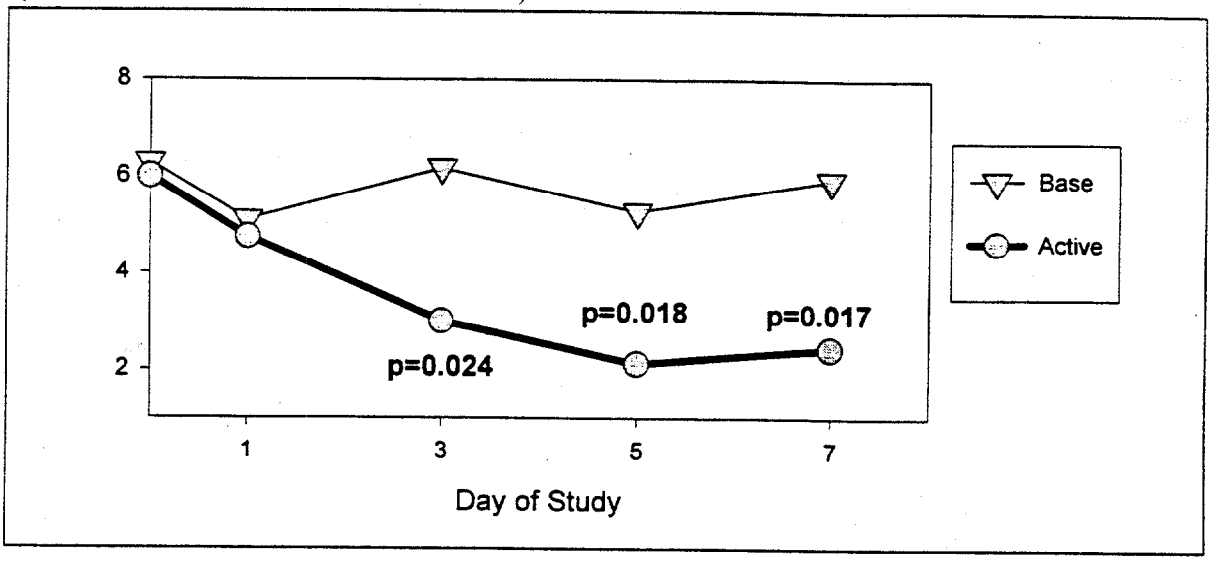


Efficacy Results for Rash Site Evaluations Stratified by Presence or Absence Of *C. albicans* at Baseline

Microbiological cultures obtained at baseline were included in Study USA and Study Australia-A. In study USA, 43% (46/106) of subjects with anal cultures at baseline showed the presence of *Candida albicans*, while 34% (36/105) of subjects with inflamed rash site cultures at baseline showed the presence of *Candida albicans*. In study Australia-A, 30% (61/202) of anal site cultures and 31% (63/202) rash site cultures showed the presence of *Candida albicans*. Both treatment groups had an equivalent number of subjects with and without *Candida albicans* at baseline. The mean total rash scores for the two treatment subsets were equivalent before treatment began (p=0.852 for subjects without *Candida albicans*; p=0.534 for subjects with *Candida albicans*).

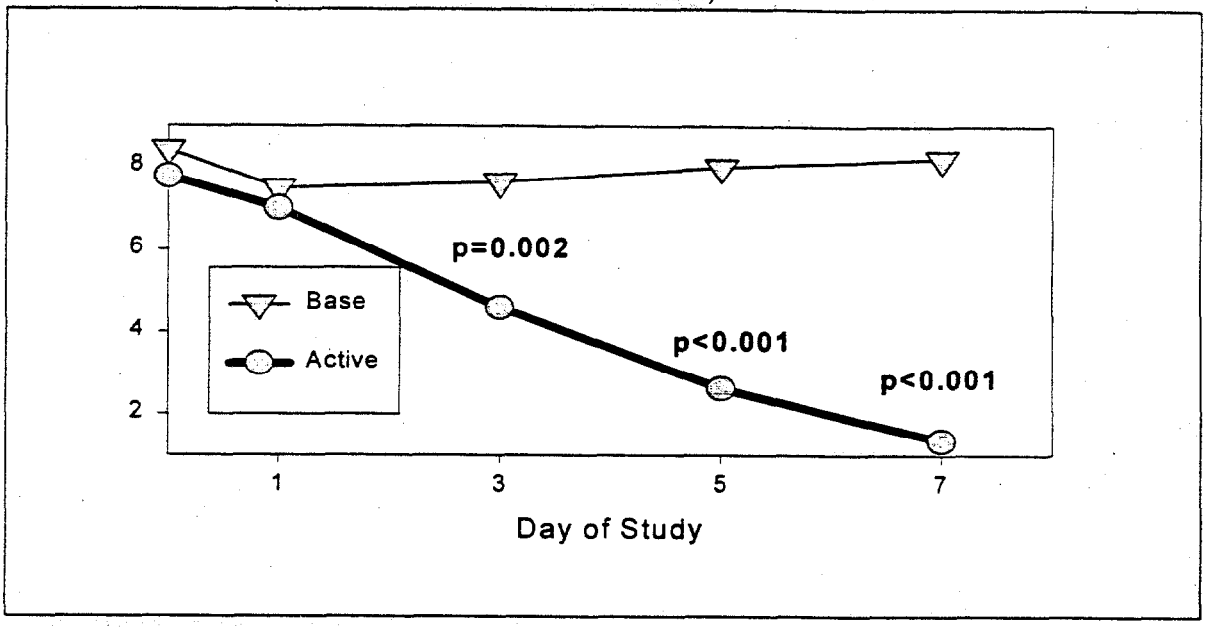
Patients with C. *albicans* demonstrated at Baseline: In Study USA, four patients in the ointment base group withdrew before completing the study because they were judged to be treatment failures. Carrying the last observation (LOCF), the active treatment was associated with significantly lower total rash scores on Study Day 3 (p=0.024), Day 5 (p=0.018) and Day 7 (p=0.017). (Figure 2A and Table 2 in Appendix A).

FIGURE 2A. MEAN TOTAL RASH SCORES IN THE PRESENCE OF CANDIDA ALBICANS AT THE INFLAMED RASH SITE AT BASELINE (EVALUABLE SUBJECTS) STUDY USA
(~17 INFANTS PER GROUP BEGAN TREATMENT)



In Study Australia-A, the active treatment had significantly lower total rash scores on Study Day 3 (p=0.002), Day 5 (p<0.001) and Day 7 (p=0.001). (Figure 2B and Table 2 in Appendix A).

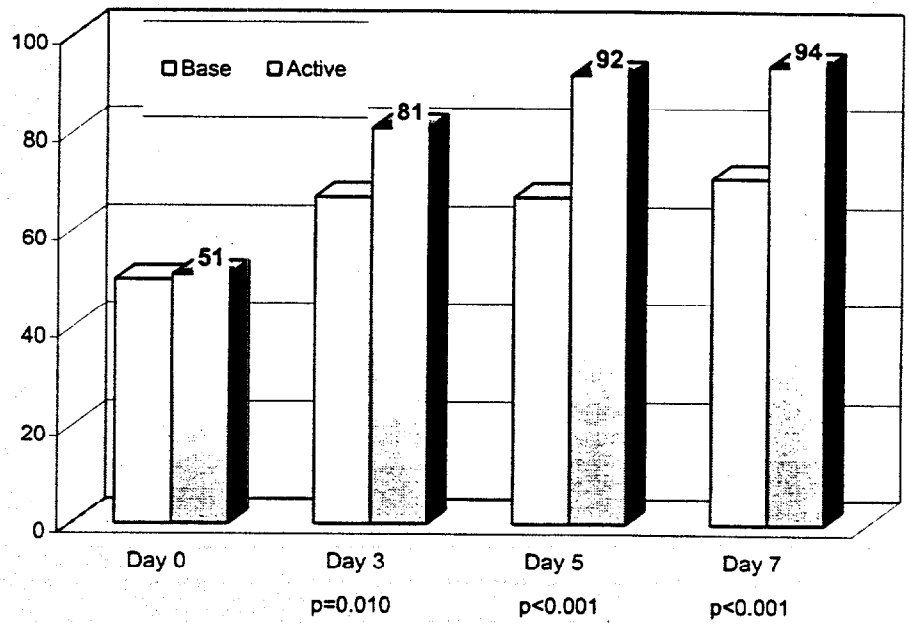
FIGURE 2B. MEAN TOTAL RASH SCORES IN THE PRESENCE OF CANDIDA ALBICANS AT THE INFLAMED RASH SITE AT BASELINE (EVALUABLE SUBJECTS) STUDY AUSTRALIA-A: (~31 INFANTS PER GROUP BEGAN TREATMENT)



Patients without C. *albicans* demonstrated at Baseline: Patients who did not demonstrate *Candida albicans* in baseline rash cultures showed a decrease in total rash score over the treatment period for both PEDIASTAT™ and the ointment base. Difference in total rash scores between baseline and the end of treatment were statistically significant for both treatment groups. However, there was little difference between the responses for PEDIASTAT™ and the ointment base when *C. albicans* was not present and the differences were not statistically significant in either study.

Efficacy Results using Global Clinical Impression
Investigators rated global clinical impression (none, mild, moderate or severe) on each study day in Studies Australia A&B. Baseline ratings were equivalent for both groups. PEDIASTAT™ proved better than the ointment base and differences were statistically significant on Study Days 3, 5 and 7. On Study Day 7, 62% of patients treated with PEDIASTAT™ had no signs of diaper dermatitis, compared to 33% of patients in the ointment base group. (Figure 3 and Table 3 in Appendix A)

FIGURE 3. GLOBAL CLINICAL IMPRESSION – SUBJECTS WITH MILD OR NO DIAPER DERMATITIS (%)



Overall Rating by Presence or Absence of *C. albicans* at Baseline in the USA Study
Few significant differences were observed between the treatment groups in the subset of evaluable subjects who showed the presence of *Candida albicans* at baseline in Study USA. More subjects in the active treatment group were cured or improved from Study Day 3 forward. However, the difference were statistical significant only on Study Day 3. In subjects who did not show the presence of *C. albicans* at baseline, the effects of the two treatments were virtually equivalent.

Overall Efficacy Discussion
The ointment base formulation has known skin protective effects and would be expected to produce improvement in diaper dermatitis. This was demonstrated in by improvement that was statistically significant in the number of rash sites, total rash score observed global clinical impression and overall rating assessments.

The active treatment was statistically superior to the ointment base for all efficacy parameters, even though the ointment base itself produced statistically significant improvement when status at the end of treatment was compared to baseline. In the overall population, significant differences between the active and ointment base groups were demonstrated as early as Day 3 for total rash scores, global clinical impression, and overall rating, and by Day 5 for number of rash sites.

When subsets of subjects were evaluated by baseline severity of diaper dermatitis, the active medication was superior to the ointment base, with significant differences

demonstrated for most subsets. Overall, infants with mild, moderate, or severe diaper dermatitis improved following treatment with 0.25% miconazole nitrate ointment.

The difference between the active and ointment base formulations was most pronounced in the subset of subjects with moderate to severe diaper dermatitis and in diaper dermatitis associated with the presence of *C. albicans*. Approximately one-third of subjects tested in these studies had *C. albicans* isolated from baseline cultures.

After seven days of treatment, *C. albicans* was observed at a significantly higher rate among subjects treated with the ointment base than with PEDIASTAT™. Moreover, significantly fewer subjects who did not have *C. albicans* at baseline in the PEDIASTAT™ group developed *C. albicans* by Study Day 7.

Efficacy Conclusions

The efficacy results of the three double-blind clinical trials clearly demonstrated that PEDIASTAT™ was effective in resolving diaper dermatitis within seven days of the start of treatment, in the absence or presence of *Candida albicans*. Moreover, PEDIASTAT™ was superior to its ointment base in treating diaper dermatitis in infants. Outcomes were consistent among all efficacy criteria.