Safety

Overall Safety Summary

Dermal testing

A total of 283 subjects participated in four (4) studies to evaluate the irritant, allergic, phototoxic and photoallergic potential of PEDIASTAT™; each used a 0-4 scale to rate reactions.

Evaluation of irritant and allergic potential (RIPT) of PEDIASTAT™

The study called for patch tests to be applied for 24 hours three times weekly for three weeks in 216 adults (28% male). There were no applications for 2 weeks, at which time there was a final, challenge application. Observed reactions were faint and minimal and occurred in 0.3% of readings in the initial phase and 1.0% in the challenge phase. The study concluded that PEDIASTAT™ has little or no irritant or allergic potential.

Evaluation of cumulative irritant potential of PEDIASTAT™

The study called for patch tests to be applied for 48 to 72 hrs three times weekly; resulting in continuous exposure for 2 weeks in 25 adults. The maximum possible score was 600. The cumulative score was zero for both PEDIASTAT™ and its vehicle. The study concluded that there was no indication of irritant or allergic potential.

Evaluation of Phototoxic potential of PEDIASTAT™

The study called for PEDIASTAT™ to be applied to the volar forearm bilaterally in 10 adults; 24 hrs later one forearm was irradiated with 3.3 J/cm2 of UVA. There were no observed reactions on either site at either 1 or 2 days after irradiation. The study concluded that there was no indication of phototoxic potential.

Evaluation of Photoallergic potential of PEDIASTAT™

The study called for PEDIASTAT™ to be applied to volar forearms twice weekly for 6 total applications to each of 32 adults. Test sites were irradiated with 3.3 J/cm2 UVA and 2 MED (up to a maximum of 168 mJ/cm2) UVB 24 hours after each application. There were no applications for 2 weeks, at which time there was a final, challenge application. After 24 hours this site was irradiated with 3.3 J/cm2 UVA and reactions were observed at 1, 2, and 3 days after irradiation. There was slight reaction in 1 subject during challenge. The study concluded that there was little or no photoallergic potential.

These tests in volunteers demonstrated little or no irritant, allergic, phototoxic or photoallergic potential.

Adverse Experiences in the Clinical Trials

There were 505 subjects participating in three Phase III efficacy studies. In each study there were two (2) treatment groups: ointment base and PEDIASTAT™. Adverse experiences were defined as any unwanted sign or symptom that occurred during the treatment period, without regard to probability of relationship to treatment. Using this definition, 77 subjects reported a total of 88 adverse experiences. Nine percent (9%) of 252 patients treated with PEDIASTAT™ had adverse experiences. Twenty one percent (21%) of 253 patients treated with ointment base had adverse experiences.

Distributing the 88 adverse experiences by organ system yields 51 % for eye, ear, nose and throat; 12% for gastrointestinal tract; 8% for general (e.g. fever); 8% for skin; 5% for the lower respiratory tract; 2% for the nervous system; 1% for the cardiovascular system and 1% for the musculoskeletal system. The distribution was quite similar for both treatment groups. All adverse experiences resolved without sequelae. (Table 4 in Appendix A presents more detailed data)

No subject treated with PEDIASTAT™ (miconazole nitrate, USP 0.25%) Diaper Rash Ointment withdrew from the clinical efficacy studies for an adverse experience (two subjects in the ointment base group withdrew).

No adverse experiences were reported at the site of treatment with PEDIASTAT™ in patients who participated in clinical development program.

Serious adverse experiences were defined as adverse experiences that were fatal, life-threatening, requiring or prolonging hospitalization, cancer, overdose, or congenital anomaly in an offspring. No serious adverse experiences were reported for 505 subjects participating in three Phase III double-blind trials or for 24 infants in the clinical pharmacology open-label uncontrolled absorption study.

Systemic Exposure

Extremely low systemic absorption was observed in a study of absorption in the infants being treated for diaper rash. In this study, blood levels after multiple daily applications of PEDIASTAT™ were below the limit of detection (detection limit of 1.0 ng/mL) in 15 of 18 subjects and were less than 5 ng/mL in 3 of 18 subjects.

For contrast, the systemic exposure observed with PEDIASTAT™ can be compared with miconazole administered intravenously. Children given 7-10 mg/kg intravenously have had

peak blood concentrations of 400-3600 ng/mL. Adults given 522 mg intravenously have had peak blood concentrations of 2020-9100 ng/mL. Thus documented blood concentrations after intravenous administration are 50 – 450 times higher in children and 275 to 1,100 times higher in adults compared to the levels observed in infants treated with PEDIASTAT™ .

Other Miconazole Formulations

No information is provided about adverse experiences reported in individuals using miconazole for topical or vaginal indication on the grounds that such formulations would not be available without prescription if the FDA had clinically significant concerns about the safety of such drugs.