2.0 Labeling

The proposed product insert for PEDIASTAT™ Diaper Rash Ointment follows.

PEDIASTAT™ Diaper Rash Ointment

Brand of miconazole nitrate ointment

For Dermatologic Use Only

DESCRIPTION

PEDIASTAT™ Diaper Rash Ointment contains the synthetic antifungal agent, miconazole nitrate (0.25%) in a zinc oxide and petrolatum base for dermatologic use. The chemical structure of miconazole nitrate is 1-[2,4-dichloro-β-{(2,4-dichlorobenzyl) oxy}phenethyl] imidazole mononitrate with empirical formula $C_{18}H_{14}Cl_4N_2O \bullet HNO_3$ and molecular weight of 479.15.

Each gram of PEDIASTAT™ Diaper Rash Ointment contains 2.5 mg of Miconazole Nitrate, USP in an hydrophobic ointment consisting of Zinc Oxide, USP, White Petrolatum, USP, trihydroxystearin and fragrance.

PEDIASTAT™ Diaper Rash Ointment is a smooth uniform white ointment.

INDICATIONS AND USAGE

PEDIASTAT™ Diaper Rash Ointment is indicated for infants with diaper dermatitis.

CLINICAL PHARMACOLOGY

Mode of Action: Miconazole nitrate has a broad *in vitro* antifungal activity against most pathogenic fungi and yeast, some Gram-positive bacilli and cocci, and certain Gram-negative organisms. This activity is based on the inhibition of the ergosterol biosynthesis in the cell membrane of the pathogenic microorganism. Imidazoles and triazoles impair the biosynthesis of ergosterol for the cytoplasmic membrane and lead to the accumulation of 14-α-methylsterols. The accumulation of ergosterol precursors and toxic peroxides results in cytolysis. The clinical efficacy of miconazole has been demonstrated against dermatophytes, *Candida* spp., *Aspergillus* spp., dimorphous fungi, *Cryptococcus neoformans, Pityrosporum* spp., and *Candida glabrata*. Susceptibility of *Candida albicans* to miconazole nitrate demonstrates a Minimal Inhibitory Concentration (MIC) ranging from 0.1 to 2.0 mcg/mL. *Candida albicans* resistance to azoles is unusual and mutation is unlikely, even with long-term exposure.

Pharmacokinetics: The topical absorption of 0.25% miconazole nitrate ointment was studied in male and female infants with diaper dermatitis ranging in age from one month to 12 months. After multiple daily applications for seven days, the plasma concentrations of miconazole were nondetectable (<1 ng/mL) in the majority (15/18) of patients and 3-3.8 ng/mL in the other three.

CLINICAL STUDIES

Three seven-day, double-blind, vehicle-controlled clinical studies were conducted. They involved a total of 505 subjects: 252 infants treated with active drug and 253 infants treated with the ointment base, which included zinc oxide and petrolatum. In those studies, PEDIASTAT™ Diaper Rash Ointment was highly effective in treating diaper dermatitis. After 1 day of therapy, infants treated with PEDIASTAT™ exhibited significant reductions in the number of rash sites and in total severity of diaper dermatitis. By the third day of treatment, infants assigned to PEDIASTAT™ exhibited total rash scores that were significantly lower than observed with infants assigned to the ointment base.

Study 1 rated diaper dermatitis at 10 body sites. Compared to ointment base, infants treated with PEDIASTAT™ had lower total rash scores on study days 3, 5 and 7 (P<0.05).

Studies 2 and 3 rated diaper dermatitis at 11 body sites and included a global clinical impression (none, mild, moderate or severe) and an overall rating compared to the previous evaluation (clinically cured, improved, no change, worse or recurred). The key results of pivotal clinical studies 2 and 3 are shown below.

Evaluation Endpoint	PEDIASTAT™ Diaper Rash Ointment	Ointment Base	p-value
Total Rash Score	Mean	Mean	
Day 0	6.93	6.79	0.796
Day 5	2.09	4.17	<0.001
Day 7	1.37 (82% Improvement)	3.85 (47% Improvement)	<0.001
Overall Rating	Infants improved or clinically cured	Infants improved or clinically cured	
Day 5	143/186 (77%)	84/184 (46%)	<0.001
Day 7	150/189 (79%)	97/177 (54%)	<0.001
Global Clinical Impression	Infants with mild or no diaper dermatitis	Infants with mild or no diaper dermatitis	
Day 5	171/186 (92%)	124/185 (67%)	<0.001
Day 7	178/189 (94%)	125/177 (71%)	<0.001

When moderate to severe diaper dermatitis was present at baseline, infants treated with PEDIASTAT™ exhibited a 79% improvement in total rash on day 7, while infants treated with ointment base improved by only 28% (P<0.001).

In studies 2 and 3, infants treated for seven days with PEDIASTAT™ had an 82% improvement in total rash, compared to a 47% improvement in the ointment base group (P<0.001).

CONTRAINDICATIONS

PEDIASTAT™ Diaper Rash Ointment is contraindicated in those patients with a history of sensitivity reactions to any of its components. It should be discontinued if hypersensitivity is noted.

PRECAUTIONS

General: If a reaction occurs, suggesting sensitivity or chemical irritation, or if the disease worsens, use of the medication should be discontinued. For external use only. Although PEDIASTAT™ Diaper Rash Ointment is not an ocular irritant, avoid introduction of PEDIASTAT™ into the eyes.

Information for Patients: See Dosage and Administration section.

Drug Interactions: Although no known drug-drug interactions have been reported during usage, drug interactions have not been formally studied.

Pregnancy/Nursing Mothers: Safety and efficacy of the product has not been established in pregnant women. Appropriate precautions should be followed when administering the product.

Pediatric Use: Although infants as young as two months were safely treated in clinical trials, use in infants below the age of three months is not recommended.

Geriatric Use: Safety and effectiveness in a geriatric population have not been established.

ADVERSE REACTIONS

Data from controlled clinical trials indicated that use of PEDIASTAT™ Diaper Rash Ointment 0.25% is associated with minimal risk of drug-related adverse experiences. Only one of 252 (0.4%) subjects in the active treatment group and two of 253 (0.8%) subjects in the ointment base group experienced cutaneous, treatment-related adverse experiences.

OVERDOSAGE

PEDIASTAT™ Diaper Rash Ointment is intended for topical use only. The risk of accidental ingestion is very low, but cannot be excluded in young children. Symptoms may include nausea, vomiting and diarrhea. Symptomatic treatment is recommended.

DOSAGE AND ADMINISTRATION

PEDIASTAT™ Diaper Rash Ointment should be applied to the entire affected area at each diaper change. Before applying the ointment, cleanse the skin with lukewarm water and pat dry. Avoid using any scented soaps, shampoos or lotions on the affected area. Gently apply PEDIASTAT™ Diaper Rash Ointment on the affected area with the fingertips. Do not rub the area as this can further irritate the skin. Thoroughly wash hands after applying PEDIASTAT™ Diaper Rash Ointment.

Clearance of the condition should begin within 3 days. However, continue treatment until there are no longer signs of rash or irritation, or for a maximum of 7 days whichever period is longer. Consult your physician if the rash becomes more severe or if the rash shows no improvement within 72 hours.

The following steps are recommended as general preventative measures for diaper rash:

1. *Check the diaper more frequently and change it at the first signs of wetness.*
2. *Expose the diaper area to air whenever possible.*
3. *Clean the area after each diaper change, wiping from front to back and use only warm water or a mild cleanser. Avoid scrubbing the site as this can further irritate the skin. Rinse well and pat dry.*

HOW SUPPLIED

PEDIASTAT™ (miconazole nitrate 0.25%) Diaper Rash Ointment is supplied in 60g and 30g tubes and 5g sample tubes.

STORAGE CONDITIONS

Store between 15°C and 30°C.

Keep out of reach of children

Ortho Dermatological
Division of Ortho-McNeil Pharmaceutical, Inc.
Raritan, New Jersey 08869

PEDIASTAT ™ is a trademark of Ortho-McNeil Pharmaceutical Corporation