



TRANSMITTED BY FACSIMILE

Mark Reeth
Assistant General Counsel
Medicis Pharmaceutical Corp
8125 North Hayden Road
Scottsdale, AZ 85258

RE: NDA # 21-159
Loprox[®] Shampoo (ciclopirox) 1%
MACMIS ID # 13727

Dear Mr. Reeth:

The Division of Drug Marketing, Advertising, and Communications (DDMAC), in conjunction with the Division of Dental and Dermatological Drug Products (DDDDP), has reviewed a patient brochure (LPX 03035) for Loprox Shampoo (ciclopirox) 1% found on the product website (<http://www.loprox.com>). The patient brochure is false or misleading because it broadens the indication and omits material facts associated with Loprox Shampoo. Thus, the patient brochure misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(a) & (n) and 321(n). These violations concern us from a public health perspective because they suggest that Loprox Shampoo is safer or more effective than demonstrated, and they encourage use in circumstances other than those for which the drug has been shown to be safe and effective. See 21 CFR 202.1(e)(6)(i).

Background

According to the FDA-approved product labeling (PI):

LOPROX Shampoo is indicated for the topical treatment of seborrheic dermatitis of the scalp in adults. [emphasis in original]

The PI also explains that Loprox Shampoo is associated with certain risks, including the following (in pertinent part):

Precautions

If a reaction suggesting sensitivity or irritation should occur with the use of LOPROX Shampoo, treatment should be discontinued and appropriate therapy instituted.

Contact of LOPROX Shampoo with the eyes should be avoided. If contact occurs, rinse thoroughly with water.

Seborrheic dermatitis may appear at puberty, however, no clinical studies have been done in patients younger than 16 years.

There is no relevant clinical experience with patients who have a history of immunosuppression (e.g., extensive, persistent, or unusual distribution of dermatomycoses, recent or recurring herpes zoster, or persistent herpes simplex), who are immunocompromised (e.g., HIV-infected patients and transplant patients) or who have a diabetic neuropathy.

Adverse Reactions

In 626 patients treated with LOPROX Shampoo twice weekly in the two pivotal clinical studies, the most frequent adverse events were increased itching in 1% of patients, and application site reactions, such as burning, erythema, and itching, also in 1% of patients. Other adverse events occurred in individual patients only.

Adverse events that led to early study medication termination in clinical trials occurred in 1.5% (26/1738) of patients treated with LOPROX Shampoo and 2.0% (12/661) of patients treated with shampoo vehicle. The most common adverse events leading to termination of study medication in either group was seborrhea. In the LOPROX Shampoo group, other adverse events included rash, pruritus, headache, ventricular tachycardia, and skin disorder. In the shampoo vehicle group, other adverse events included skin disorder and rash.

In addition, the Dosage and Administration section of the PI states, "Treatment should be repeated twice per week for 4 weeks, with a minimum of 3 days between applications. If a patient with seborrheic dermatitis shows no clinical improvement after 4 weeks of treatment with LOPROX Shampoo, the diagnosis should be reviewed."

DDMAC had previously objected, in an untitled letter dated March 7, 2000, to the dissemination of visual aids LPX37899 and LPX35998, LPX36999 (a product monograph), and a note pad that contained claims for unapproved uses of Loprox Cream and Lotion. Nevertheless, you continue to promote Loprox in a violative manner.

Broadening of Indication

The patient brochure presents numerous claims that Loprox Shampoo is effective for long-term, maintenance treatment of seborrheic dermatitis. For example:

- "While seborrheic dermatitis is a chronic condition and cannot be prevented or cured, it can be effectively managed with ongoing treatment." (page 3)
- "Make LOPROX Shampoo a simple part of your weekly routine." (page 6)
- "Seborrheic dermatitis is a chronic condition, so continued use is important." (page 6)
- "If used regularly, LOPROX Shampoo can help you keep your condition under control." (page 6)
- "Without regular treatment, seborrheic dermatitis can reappear without warning." (page 7)
- Graphic of a prescription for a 120 mL bottle of Loprox Shampoo with 6 refills. (page 7)

- o Graphics of 8 weekly “diaries” for the patient to keep track of his or her treatment schedule. (pages 8-11).

These claims and presentations contribute to the misleading impression created by the piece as a whole that Loprox Shampoo is safe and effective for chronic, long-term (maintenance) treatment of seborrheic dermatitis when, to our knowledge, this indication has not been demonstrated by substantial evidence or substantial clinical experience. When considered collectively, claims such as making “LOPROX shampoo a simple part of your weekly routine” (among others), the graphic of an eight week dosing diary, and the graphic of a prescription for Loprox Shampoo that includes six refills (which corresponds to 42 weeks of treatment) all promote the use of Loprox Shampoo for chronic treatment.

As you know, FDA considers such claims unsupported. In a letter dated August 5, 2005, DDDDP informed Medicis that Medicis' supplemental NDA application seeking approval of a [] indication for Loprox Shampoo was not approvable. DDDDP stated that Medicis had failed to provide substantial evidence of efficacy to support a maintenance treatment indication because only one of the two trials submitted showed a reduction in relapse rate for patients treated with Loprox. Furthermore, the Clinical Studies section of the PI discusses two randomized, double blind clinical trials in which patients were treated for **only 4 weeks**.

Omission of Material Fact

Promotional materials are also false or misleading if they fail to reveal facts that are material in light of the representations made in the materials or with respect to the consequences that may result from the use of the drug as recommended or suggested in the materials. The patient brochure omits material facts because it fails to provide important risk information. Although the patient brochure presents several effectiveness claims for Loprox Shampoo, it fails to include the most serious risks from the PI. The only risk information included in this patient brochure is excerpted from the Adverse Reactions section of the PI. By omitting the most serious risks associated with the drug, the patient brochure misleadingly suggests that Loprox Shampoo is safer than has been demonstrated.

Additionally, the piece presents a claim relating to pediatric populations without revealing material facts about Loprox's indicated patient population. Specifically, page 4 notes that “...this condition usually starts during puberty. Seborrheic dermatitis of the scalp can also affect infants.” However, Loprox is only indicated for adults and has not been studied in these other populations; as the Precautions section of the PI states, “Seborrheic dermatitis may appear at puberty, however, no clinical studies have been done in patients younger than 16 years.” This material fact is not revealed anywhere in the brochure. We note the indication is presented on page 5 but this does not correct the misleading impression created by the presentation on page 4 that Loprox is approved for use in patients younger than 16 years.

Conclusion and Requested Action

For the reasons discussed above, the patient brochure impermissibly broadens the indication and omits material facts associated with Loprox Shampoo. Accordingly, the patient brochure misbrands Loprox Shampoo in violation of the Federal Food, Drug, and Cosmetic Act (Act). See 21 U.S.C. 352 (a) & (n), 321 (n) and 21 CFR 202.1(e)(6)(i).

DDMAC requests that Medicis immediately cease the dissemination of violative promotional materials for Loprox Shampoo such as those described above. Please submit a written response to this letter on or before January 18, 2006, stating whether you intend to comply with this request, listing all violative promotional materials for Loprox Shampoo such as those described above, and explaining your plan for discontinuing use of such materials.

Please direct your response to the undersigned at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD, facsimile at 301-796-9878. In all future correspondence regarding this matter, please refer to MACMIS # 13727 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Loprox Shampoo comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Suzanne Berkman, PharmD
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Suzanne Berkman
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