TRANSMITTED VIA FACSIMILE

MAR - 5 1999

Stephenie Barba
Executive Director
Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

RE: **NDA # 20-539**
Lamisil (terbinafine HCl) Tablets
MACMIS # 6614

Dear Ms. Barba:

This letter concerns Novartis' dissemination of promotional labeling and advertising for Lamisil (terbinafine HCl) tablets. On February 4, 1999, we sent correspondence to you, requesting information about the preparation and submission of a detail aid based on an abstract of a study known as the *Continuous Terbinafine vs. Intermittent Itraconazole in the Treatment of Toenail Onychomycosis Study* (L.I.ON Study). On February 18th, you replied that the detail aid in question originally appeared as a poster at a medical conference and was subsequently reprinted by Novartis. The abstract was then made available to the Novartis Medical Services department and to the Novartis sales representatives. You submitted this detail aid based on the L.I.ON Study to DDMAC on Form 2253 on November 17, 1998.

Based on a review of this detail aid, we have determined that Novartis has disseminated labeling materials for Lamisil that contain false or misleading statements or suggestions in violation of the Federal Food, Drug, and Cosmetic Act.

Dissemination of Misleading Detail Aid Containing Portions of the L.I.ON Study

Your detail aid for the promotion of Lamisil consists of an edited report of an abstract of an unpublished interim comparative study involving Lamisil and Sporanox, entitled: *"Terbinafine vs. Intermittent Itraconazole in the Treatment of Toenail Onchomycosis (L.I.ON Study),"* [presented at a Meeting entitled "Focus on Fungal Infections," held on March 4-6, 1998, in Orlando, Florida]. This detail aid contains only selected portions of the L.I.ON Study and is misleading for the following reasons:

- **Use of Selectively Edited and Incomplete Study Results**

In the detail aid about the L.I.ON Study, clinical trial information is selectively presented,[1] and statements that Lamisil was clinically superior are also made.[2] However, the information in the detail aid is based on an incomplete trial, with therapeutic results being measured at only one interim time point (week 48), in an ongoing 72-week study.

- **Comparative Superiority Claim based on a Comparison of an Approved Use of Lamisil With an Unapproved Use of Sporanox**

Both Sporanox and Lamisil are safe and effective treatments for toenail onychomycosis, when used as labeled. A pulsed dosing regimen of Sporanox has also been approved as safe and effective for the treatment of fingernail onychomycosis, but not for toenail onychomycosis.

The results of the interim L.I.ON study you disseminated, state that *continuous* Lamisil therapy is more efficacious than *pulsed* Sporanox therapy in the treatment on toenail onychomycosis.[3] Thus, the study compares an approved use of Lamisil to an unapproved use of Sporanox to allege that Lamisil is superior. A disclaimer at the bottom of page 1 of the detail aid stating that "Intermittent Dosing of Itraconazole is not an approved treatment regimen for toenail onychomycosis in the United States" cannot correct this misleading comparative superiority claim.

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1 The detail aid referenced consists of four pages containing bulleted paragraph summaries of the L.I.ON Study Abstract, Background, Objective, Study Design, Results, Conclusions, and References. The piece is identified as LMT-9144-P37051904.

2 Novartis Detail Aid (p.1): "Terbinafine administered continuously for 12 or 16 weeks was more effective than intermittent therapy with itraconazole given for 1 week every 4 weeks for 12 or 16 weeks for the treatment of onychomycosis."

3 "The study results complement the findings of former double-blind studies in which continuous terbinafine therapy is more effective than both intermittent and continuos itraconazole therapies in the treatment of onychomycosis." at p.1 of the Novartis L.I.ON Study Detail Aid.

4 "The study results complement the findings of former double-blind studies in which continuous terbinafine therapy is more effective than both intermittent and continuos

- **Misleading Presentation of Mycological Cure Rate**

  You present two graphs as part of the report of the L.I.ON Study (Detail Aid). These graphs show comparative mycological cure rates between terbinafine and itraconazole treatments at 48 weeks, as well as the comparative median time to mycological cure. These graphs are misleading because they do not prominently disclose that the mycological cure rate is not predictive of the total clinical cure rate, which may be lower. In addition, the mycological cure rates presented in these graphs do not disclose that these rates may be lowered by the inclusion of relapse rates expected to occur throughout the completion of the study (week 72). [5]

- **Additional Efficacy Claims Unsupported by Cited Reference**

  You conclude that the L.I.ON Study *"..and other studies, taken together,"* [emphasis added] suggest that continuous terbinafine is more effective than both intermittent and continuous itraconazole for the treatment of onychomycosis." This conclusion is false or misleading and clearly not supported by the L.I.ON study for the following reasons:

  a. The L.I.ON Study did not compare itraconazole <u>continuous</u> therapy with terbinafine <u>continuous</u> therapy.

  b. The L.I.ON Study was limited only to toenail onychomycosis.

  c. The phrase "other studies taken together" does not identify which additional studies you rely upon in conjunction with the L.I.ON study to make the claim of superiority of continuous terbinafine over continuous itraconazole in the treatment of onychomycosis.

- **Lack of Fair Balance**

  The detail aid promotes the efficacy of Lamisil, and presents the efficacy rate of mycological cure and conclusions of clinical superiority in written and graphic

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itraconazole therapies in the treatment of onychomycosis." at p.1 of the Novartis L.I.ON Study Detail Aid.

5 The approved product labeling of Lamisil discloses a relapse rate of approximately 15% at one year after completion of Lamisil therapy. Relapse rates are not discussed in conjunction with the efficacy rates presented in your (L.I.ON Study) detail aid.

format. However, the detail aid does not contain any disclosure of risks associated with the use of Lamisil. Therefore, the presentation of the detail aid lacks fair balance.

Conclusion and Requested Action

The materials that you disseminated contain false and/or misleading information about the safety and efficacy of Lamisil. In order to address these objections, you should immediately discontinue the promotional use of these pieces and all other materials that contain the same or similar violations. You should respond in writing to this letter by March 15, 1999.

If you have any questions or comments, please contact the undersigned by facsimile at (301) 594-2828, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, Rm. 17-B-04, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official. In all future correspondence regarding this particular matter, please refer to MACMIS ID # 6614 in addition to the NDA number.

Sincerely,

/S/

Patricia Kuker Staub, Esq. R.Ph.
Regulatory Counsel for the
Division of Drug Marketing,
Advertising and Communications