



TRANSMITTED BY FACSIMILE

Cheryl A. Elder, Pharm.D.
Associate Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

RE: NDA 20-539
Lamisil® (terbinafine hydrochloride) 250 mg Tablets
MACMIS ID#: 11692

Dear Dr. Elder:

This letter informs Novartis Pharmaceuticals Corporation (Novartis) that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has found certain promotional materials for Lamisil (terbinafine hydrochloride) Tablets to be in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. Specifically, the “It’s Alive – Digger” 60-second direct-to-consumer (DTC) broadcast television (TV) advertisements (ads) are false or misleading because they overstate Lamisil’s efficacy, minimize risk information, and make an unsubstantiated superiority claim. Our specific objections follow:

Overstatement of Efficacy

The TV ads are misleading because they represent or suggest that Lamisil is more effective than has been demonstrated by substantial evidence or substantial clinical experience (see 21 CFR 202.1(e)(6)(i)).

The TV ads overstate the efficacy of Lamisil through their visual portrayal of the clinical effects of Lamisil and the failure of the ads to accurately portray the efficacy rates for the drug. Specifically, the TV ads depict onychomycosis, a toenail infection, represented by “Digger,” an animated dermatophyte microorganism, and illustrate an exaggerated visual effect of Lamisil’s efficacy, that is not corrected by the weak SUPERS provided in the ads, as described below.

In the ads, Digger infects a toenail, invites a few dermatophyte friends to join him and then “settles in.” The infection progresses as more and more dermatophytes appear alongside Digger and the color of the nail bed changes from a healthy pink to an infected and unhealthy brown color. Over the “horizon,” a giant-sized Lamisil tablet appears, attacking and ultimately defeating the infection as it repeatedly rolls back and forth over Digger. As the camera pans back, Digger appears to have been beaten by the Lamisil tablet as he groans and slowly crawls away, thereby eradicating the infection.

The nail bed has completely changed back to the healthy and non-infected pink color it was before the infection commenced. Accompanying this vivid efficacy presentation is an audio voiceover (VO) promoting Lamisil, “Unlike surface treatments, Lamisil is a pill that works through the bloodstream...to target and attack the infection at its source, underneath the nail. In fact, you can start to see clearer, healthier nails in just three months.”

The ads’ strong visuals and claims and weak SUPERS combine to give a misleading picture of the efficacy of Lamisil and the time required for clinical success. The ads portray both a “mycological cure” (i.e., **all** dermatophytes, including Digger, are gone after the arrival of the giant Lamisil tablet) and a “clinical cure” (the pink healthy toe, minus all traces of affected nail), thus implying complete effectiveness for all or most patients. These representations in the ads are not representative of the clinical trial results. Furthermore, FDA is not aware of additional data to support these claims of guaranteed and complete efficacy. Specifically, the Clinical Studies section of the approved package labeling (PI) states:

“Results of the first toenail study...demonstrated...[f]ifty-nine percent (59%) of patients experienced effective treatment (mycological cure plus 0% nail involvement or >5mm of new unaffected nail growth); 38% of patients demonstrated mycological cure plus clinical cure (0% nail involvement).”

“In a second toenail study of dermatophytic onychomycosis...similar efficacy against the dermatophytes was demonstrated.”

“The mean time to overall success was approximately 10 months for the first toenail study and ... for patients evaluated at least six months after achieving clinical cure and at least one year after completing Lamisil therapy, the clinical relapse rate was approximately 15%.”

Your ads do not adequately communicate that, in fact, only 38% of patients in clinical trials achieved complete effectiveness or cure of their condition (i.e., a mycological cure plus a clinical cure) and some of those patients relapsed. Moreover, your qualifying SUPER “It takes about 10 to 12 months for new nails to grow in. Results may vary” precedes your efficacy claims. Because of the lag time between the SUPER and your claims of Lamisil’s effectiveness, the presence of an intervening and unrelated SUPER with the telephone number, and the lack of comparative emphasis placed on this information, it is unlikely that consumers will strongly associate this qualification with the claims of effectiveness in the audio and visuals of your ads. Therefore, your SUPER would have to be appropriately placed and substantially more prominent, and your ads would need to be qualified with additional efficacy context, to overcome the message conveyed by the dominant visual graphics and audio claims that suggest a greater drug efficacy than demonstrated.

Minimization of Risk

The TV ads fail to clearly communicate the major risks associated with the use of Lamisil therapy. The compelling and attention-grabbing visuals and other competing modalities, such as background music, VOs, and SUPERS, occurring simultaneously during presentation of the risk information in the TV ads distract from and may make it difficult for consumers to adequately process and comprehend the risk information. The effect is to minimize these risks and thus suggest that Lamisil is safer than

has been demonstrated by substantial evidence or substantial clinical experience (see 21 CFR 202.1(e)(6)(i)).

Specifically, the presentation of competing visual, graphics, and audio distractions interferes with the simultaneous audio description of the major risks: “Lamisil isn’t for people with liver or kidney problems. Rarely, serious side effects in the liver or serious skin reactions have occurred, so your doctor may do a simple blood test. Other side effects including headache, diarrhea, indigestion and rash, were generally mild.” The sequence in which the most important risk information is described features the giant-sized Lamisil tablet attacking and defeating Digger in the infected toenail bed with compelling imagery and sound effects (i.e., after the Lamisil tablet rolls over Digger's tail, the giant-sized Lamisil tablet continues to slowly roll back and forth over Digger in an attention-grabbing pendulum motion). As the camera pans back from the rolling Lamisil tablet action, viewers hear Digger groaning as he tries to crawl away but finally collapses while the nail bed changes color from infected-brown to healthy-pink. The distracting animated visuals and sound effects hamper communication of the risk information. In addition, SUPERS appear on the bottom of the screen during this busy activity, thus further distracting from this important information. For example, during one version of the ad, a competing SUPER related to the efficacy of the product (i.e., “It takes about 10 to 12 months for new nails to grow in. Results may vary.”) appears during the audio presentation of the risk information that “Lamisil isn’t for people with liver or kidney problems,” and at the same time the Lamisil tablet rolls over Digger’s tail. The juxtaposition of these competing and directly contradictory audio/risk and textual/efficacy messages, with the further distraction of the video elements, would have to be changed to avoid undermining the communication of both of these important messages.

Unsubstantiated Superiority Claims

The TV ads are misleading because they contain a drug comparison that represents or suggests that Lamisil is more effective than other prescription drug products when such has not been demonstrated by substantial evidence or substantial clinical experience (See 21 CFR 202.1(e)(6)(ii)). In the ads, you claim:

- “It’s **the number 1 brand** for treating infected nails.” (emphasis added)

This claim is accompanied by a large graphic numeral “1” on the screen. These audio and visual claims suggest to consumers that Lamisil is the most effective treatment for “infected nails,” not merely that your drug is the “number 1 prescribed brand” for the condition, which may be supported by your data. FDA is not aware of substantial evidence or substantial clinical experience to support the claim that Lamisil is more effective than other prescription drug products for the treatment of onychomycosis.

Conclusion and Requested Action

These TV ads are violative of Section 502(n) of the Act and its implementing regulations. Novartis should immediately cease broadcast of these TV ads, as well as all other promotional materials for Lamisil that contain the same or similar claims and presentations. Please submit a written response to DDMAC on or before September 8, 2003, describing your intent and plans to comply with the above

Cheryl A. Elder, Pharm.D.
Novartis Pharmaceuticals Corporation
NDA 20-539/MACMIS #11692

4

requests. In your letter to DDMAC, please include a complete list of all discontinued promotional materials and the date of their discontinuation.

Please direct your response to the undersigned by facsimile at (301) 594-6759, or by writing to the Food and Drug Administration, DDMAC, HFD-42, Room 8B-45, 5600 Fishers Lane, Rockville, Maryland 20857. In all future correspondence on this matter, please refer to MACMIS #**11692** and NDA **20-539**. DDMAC reminds Novartis that only written communication is considered official.

Sincerely,

{See appended electronic signature page}

Jennifer C. Murphy, Pharm.D.
Consumer Promotion Analyst
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/

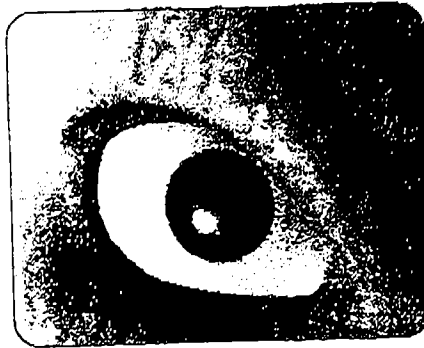
Christine Smith
8/22/03 03:55:31 PM
Signed for Jennifer C. Murphy

IT'S ALIVE
PAGE 1
:60

FINAL AS PRODUCED - 4/1/03

ACTION:

Open on close-up of "Digger" as he introduces himself.

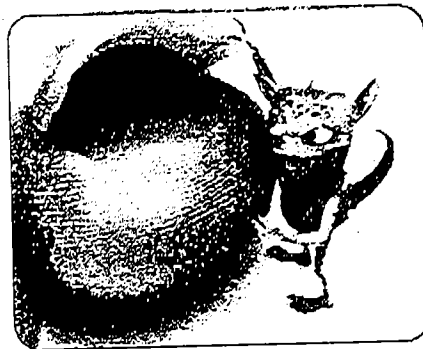


ANIMATED CHARACTER:

Oh hey, hi. I'm Digger. Don't mind me. I'm just a dermatophyte.

You know, a nail infection.

He lifts the nail and slides under it, into the nail bed, dramatizing the way a toenail fungus enters your nailbed.



All I want is to get in here and live under your nail.



You can't get me with clippers, or those surface treatments you try on your own.

I'm in too deep in your nail bed.

Digger travels deeper into the nail bed and settles in and invites his friends—fellow dermatophytes—who infect the nail bed and toenail.



I'll make myself comfortable...

ACTION:

As Digger gets comfortable, his friends pull and tear at the tissue underneath the nail, and the nail tissue begins to change color to communicate infection.



Invite a few friends.
Settle in.

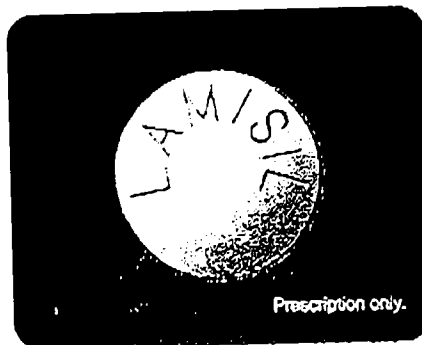
We see an image of a human foot with two toenails infected with mild toenail fungus.



AVO:
Do you have thick,
discolored or flaky nails?

Millions of people do.

It may be caused by an
active, live infection.



That's why you should
ask your doctor about
prescription-only
Lamisil.

As the dermatophytes continue to infect the tissue, little specs can be seen as they dig. The entrance of the pill begins to clear up the nail bed and the dermatophytes exit, leaving only one.



Unlike surface
treatments,
Lamisil is a pill that
works through the
bloodstream . . .

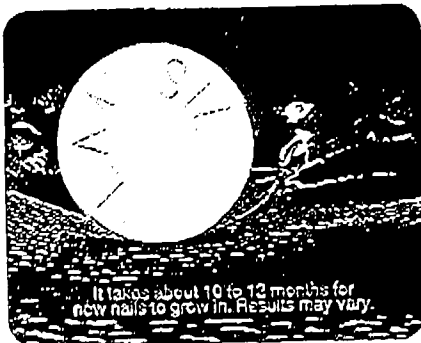
ACTION:

The Lamisil pill interacts with Digger the Dermatophyte by pinning his tail and rolling over him, leaving Digger as a defeated fungus.

SUPER:

It takes about 10 months for new nails to grow in.

Results may vary.

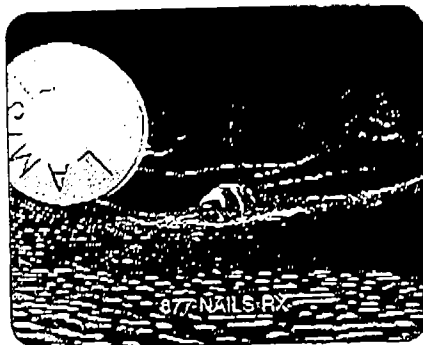


... to target and attack the infection at its source, underneath the nail.

In fact, you can start to see clearer, healthier nails in just three months.

SUPER:

877-NAILS-RX

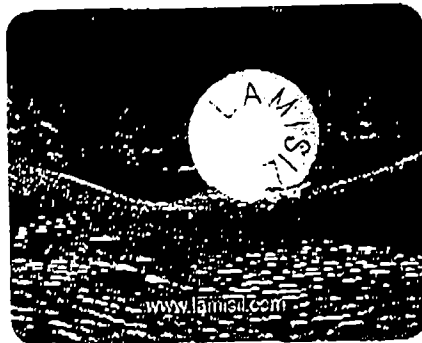


AVO:

Lamisil isn't for people with liver or kidney problems.

SUPER:

www.lamisil.com



Rarely, serious side effects in the liver or serious skin reactions have occurred,

SUPER:

See our ad in Health Magazine.



so your doctor may do blood tests. Other side effects, including headache, diarrhea, indigestion and rash, were generally mild.

ACTION:

Defeated dermatophyte slowly crawls away.

SUPER:

Ask your doctor.



Ask your doctor
about Lamisil.

ACTION:

"Number One" super appears over pill and as we pull away from the nail bed and outside of the toe, the number one becomes the "I" in the brand name Lamisil on the end-frame.



It's the #1 brand
for treating infected
nails.

SUPER:

*Get your nail
infection where it
grows.*



Once-daily
Lamisil tablets.
Get your nail
infection where it
grows.