WASHINGTON LEGAL FOUNDATION
2009 Massachusetts Avenue, N.W.
Washington, DC 20036
202 588-0302

May 1, 2007

By Facsimile [301-796-9877]
and First-Class Mail

Thomas Abrams, RPh, MBA
Director
Division of Drug Marketing, Advertising, and Communications
10903 New Hampshire Ave.
Bldg 22 Rm 1400
Silver Spring, MD 20993-0002

Re: NDA # 20-965
Levulan® Kerastick® (aminolevulinic acid HCl) for Topical Solution, 20%
MACMIS # 15170

Dear Mr. Abrams:

On April 20, 2007, the Division of Drug Marketing, Advertising, and Communications (DDMAC) sent a warning letter to DUSA Pharmaceuticals, Inc. (DUSA) alleging that an advertisement for Levulan Kerastick (aminolevulinic acid HCl) for Topical Solution, 20% contains inadequate risk information and overstates the drug's indication and efficacy and therefore "misbrands the drug in violation of" 21 U.S.C. §§ 352(n) and 321(n). For the reasons discussed below, DDMAC should withdraw the warning letter.[1]

Problematic Policy of Requiring Double Disclosure of Risk and Other Information

DDMAC alleges that the advertisement is misleading because it "entirely omits risk information." This allegation is unsupportable because the advertisement in fact contains the very information that DDMAC claims is absent. Complete risk information appears in the full prescribing information attached to the "creative" part of the advertisement, as DDMAC acknowledges. This allegation is therefore factually untenable.

[1] In previous correspondence with you, we have listed all of the previous letters in which we explained our objections to DDMAC's efforts to regulate the content of prescription drug communications. For the sake of brevity, we are discontinuing that practice. All of the concerns WLF is raising in this letter to you have been raised before.

DDMAC has a well-established policy of ignoring the brief summary in evaluating whether prescription drug advertisements disclose important information, such as risk information and the complete labeled indication. This policy effectively requires manufacturers to present this information twice—once in the "creative" part and again in the brief summary. This approach is legally vulnerable, and inconsistent with broader FDA policies. We have described these deficiencies repeatedly and in detail in previous correspondence with you, and in a citizen petition that WLF has submitted to FDA. *See* Docket No. 2006P-0319.

Problematic Risk Minimization Allegation/Unsubstantiated Allegations of Misleadingness

DDMAC objects to the statement that Levulan Kerastick treats actinic keratoses (AKs) without weeks of red, raw skin on the ground that the statement conflicts with the approved labeling. According to that labeling, erythema (redness associated with capillary dilation) and edema resolved to baseline or improved within four weeks after therapy. DDMAC appears to believe that the advertisement is misleading because it implies that redness subsides in less than weeks when, according to the labeling, it can take up to four weeks for this side effect to resolve.

DDMAC's letter fails to reproduce important qualifying information that accompanies this claim. The advertisement states not only that Levulan Kerastick treats AKs without weeks of red, raw skin, but also that "skin response usually subsides within a week of treatment, with a transient sunburn-like redness." The advertisement therefore makes clear that redness is an adverse event associated with this product, and that the redness can last for up to four weeks. This is entirely consistent with the labeling. Moreover, the brief summary accompanying the "creative" part of the advertisement discusses erythema in detail. Under the circumstances, it is hard to see how DDMAC could credibly contend that any person viewing the advertisement would be misled with respect to the duration of erythema in patients treated with this product.

Indeed, DDMAC does not explain how it determined that this statement had the meaning attributed to it. As WLF has explained in detail in previous correspondence and in our citizen petition, there are often plausible alternatives to the interpretations posited by DDMAC. Moreover, there are important statutory and constitutional limitations on DDMAC's authority to regulate protected speech based solely on an uncorroborated opinion about the meaning of that speech. These issues are fully addressed in our previous submissions.

Untenable Allegation of Broadened Indication

DDMAC asserts that the reference to "AK" in the "creative" part of the advertisement misleadingly implies that Levulan Kerastick "is useful for the treatment of all patients with actinic keratoses when this is not the case." This assertion cannot be supported.

As with the risk information that DDMAC claims is omitted from the advertisement, the complete labeled indication for this product appears in the second page of the advertisement. DDMAC's policy of requiring disclosure of information already appearing in one part of the advertisement in another part of the advertisement as well is vulnerable for the same reasons discussed above in connection with the presentation of risk information. WLF has repeatedly set

forth the serious issues raised by this approach in previous correspondence with you and in our citizen petition.

Lack of Guidance on Patient Preference Claims

Finally, DDMAC contends that the patient preference claim in the advertisement ("4 out of 5 patients prefer Levulan to previous 5-FU treatments") is misleading because of deficiencies in the cited study. According to DDMAC, this claim can only be used if "based on evidence from an adequate and well-controlled study or studies using validated and well-developed instruments . . . ." This contention, like the others in the letter, presents important issues.

First, DDMAC's position in this letter reflects a well-established policy, also evidenced in many other letters, of prohibiting manufacturers from using data or other information from sources other than those deemed acceptable by DDMAC. We have set forth the reasons that this policy is legally questionable in previous correspondence with you and in our citizen petition.

Second, it is improper for DDMAC to object to patient preference claims when FDA has issued no guidance on the manner in which such claims should be substantiated or presented. DDMAC's statement that such claims require support from "an adequate and well-controlled study or studies using validated and well-developed instruments" provides no meaningful guidance and establishes an unreasonably and indefensibly high bar. For example, both the Federal Food, Drug, and Cosmetic Act and FDA regulations make clear that prescription drug promotional claims are not always required to be supported by "substantial evidence." *See* 21 U.S.C. § 352(a) ("competent and reliable scientific evidence"); 21 C.F.R. § 202.1(e)(6)(ii) ("substantial clinical experience").

We have previously corresponded with you regarding the legal issues presented by the use of warning and untitled letters to establish binding legal norms. DDMAC should employ the procedures prescribed by law to issue regulations or guidance documents addressing patient preference claims and other types of claims for which manufacturers require guidance (*e.g.*, pharmacoeconomic claims). Until such regulations or guidance documents are issued, DDMAC should refrain from using warning and untitled letters to provide its views to the manufacturers regarding the appropriate treatment of these claims.

Conclusion and Requested Action

We request that DDMAC immediately withdraw the warning letter to DUSA concerning Levulan Kerastick. We urge DDMAC to cease the issuance of warning and untitled letters and advisory correspondence that contain allegations the same as or similar to those described above.

The deficiencies described in this letter do not necessarily constitute an exhaustive list. DDMAC must ensure that its actions with respect to prescription drug promotion, and to other forms of commercial speech, comply with the First Amendment, and do not exceed FDA's statutory authority under the Federal Food, Drug, and Cosmetic Act.

Sincerely,

Richard A. Samp
Chief Counsel

cc: Sheldon Bradshaw (GCF-1)