DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Peter A. Lankau
President and CEO
Endo Pharmaceuticals Inc.
100 Endo Boulevard
Chadds Ford, PA 19317

RE: **NDA 20-612**
Lidoderm® (Lidocaine Patch 5%)
MACMIS # 13494

WARNING LETTER

Dear Mr. Lankau:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) in the U.S. Food and Drug Administration (FDA) has reviewed two professional direct mailing pieces (identified as LD-1204F and LD-1316B) for Lidoderm® (Lidocaine Patch 5%) submitted by Endo Pharmaceuticals Inc. (Endo) under cover of Form FDA 2253. The direct mailing pieces are false or misleading for several reasons: first, they contain unsubstantiated effectiveness claims for Lidoderm; second, they omit and minimize serious risk information associated with Lidoderm; and third, they fail to communicate an important limitation in the drug's FDA-approved indication. Thus, the direct mailing pieces misbrand the drug within the meaning of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(a) and 321(n). These violations are a public health concern because they may encourage use of Lidoderm in circumstances other than those in which the drug has been shown to be safe and effective.

Background

Approved Product Labeling

Lidoderm (Lidocaine Patch 5%) is a topical anesthetic patch comprised of an adhesive material containing 5% lidocaine. According to its FDA-approved product labeling (PI):

> LIDODERM is indicated for relief of pain associated with post-herpetic neuralgia [PHN]. It should be applied only to **intact skin**. (emphasis in original).

The PI also states that Lidoderm is associated with numerous important risks, including the following (in pertinent part):

> **CONTRAINDICATIONS**
> LIDODERM is contraindicated in patients with a known history of sensitivity to local anesthetics of the amide type, or to any other component of the product.
>
> **WARNINGS**
> **Accidental Exposure in Children**
> Even a *used* LIDODERM patch contains a large amount of lidocaine (at least 665 mg). The potential exists for a small child or a pet to suffer serious adverse effects from chewing or ingesting a new or used LIDODERM patch, although the risk with this formulation has not been evaluated. It is important for patients to **store and dispose of LIDODERM out of the reach of children and pets.**
>
> **Excessive Dosing**
> Excessive dosing by applying LIDODERM to larger areas or for longer than the recommended wearing time could result in increased absorption of lidocaine and high blood concentrations, leading to serious adverse effects (see ADVERSE REACTIONS, Systemic Reactions).
>
> **PRECAUTIONS**
> **General**
> ***Hepatic Disease***: Patients with severe hepatic disease are at greater risk of developing toxic blood concentrations of lidocaine, because of their inability to metabolize lidocaine normally.
>
> **Drug Interactions**
> ***Antiarrhythmic Drugs***: LIDODERM should be used with caution in patients receiving Class I antiarrhythmic drugs (such as tocainide and mexiletine) since the toxic effects are additive and potentially synergistic.
>
> **ADVERSE REACTIONS**
> **Application Site Reactions**
> During or immediately after treatment with LIDODERM (lidocaine patch 5%), the skin at the site of application may develop erythema, edema, bruising, papules, vesicles, discoloration, depigmentation, burning sensation, pruritus, dermatitis, petechia, blisters, exfoliation, or may be the locus of abnormal sensation. These reactions are generally mild and transient, resolving spontaneously within a few minutes to hours.

Regulatory History

On November 24, 1999, DDMAC sent you an untitled letter regarding a previous sales aid for Lidoderm that omitted and minimized risk information, including important information from the “Accidental Exposure in Children” and the “Excessive Dosing” warnings (see above).

Unsubstantiated Effectiveness Claims

Both of the mailing pieces at issue in this letter make effectiveness claims for Lidoderm that, to our knowledge, have not been demonstrated by substantial evidence or substantial clinical experience. For example, the first piece (LD-1204F) presents the following claims:

- 66% of patients (n=310) reported improvement in pain intensity at week 1
- 78% of patients (n=310) reported improvement in quality of life at week 1

The second piece (LD-1316B) presents the following claims:

- **2** out of **3** patients (n=310) achieved reduction in pain intensity at **week 1**
  - No serious systemic adverse events were seen in this predominantly elderly population (mean age 71 years)
- Continue with LIDODERM® and more of your patients may respond
- **4** out of **5** patients (n=310) achieved reduction in pain intensity at **week 2**, with efficacy sustained for the duration of the trial

These claims are misleading because they are not supported by substantial evidence or substantial clinical experience. The study cited for support of these claims was an open-label, single-arm study with no concurrent control group, rather than a well controlled study.[1] Without a control group and blinding to reduce the possibility of bias, subjective endpoints such as "pain intensity" and "quality of life" cannot be properly assessed. It is therefore not possible to tell from the study whether patient outcomes on Lidoderm were better than what would be expected in the absence of treatment. Furthermore, we are not aware of any other evidence or clinical experience that substantiate your claims.

Omission of Risk

Both of the direct mailing pieces present numerous effectiveness claims for Lidoderm, including "improvement in pain intensity," "improvement in quality of life," "relief of the neuropathic pain of PHN," "Pain relief is within reach!," "for localized pain relief," and "With LIDODERM…it all adds up to relief." Under the Act, whether a drug's labeling is misleading depends not only on the representations made or suggested in it, but also on the extent to which the labeling fails to reveal facts material in light of those representations. See 21 U.S.C. 321(n) and 352(a). In this instance, both pieces fail to include such information. Specifically, they fail to reveal important risks associated with use of Lidoderm as presented in the PI (above). For example, both pieces omit the serious warnings set forth above regarding accidental exposure in children and excessive dosing.

[1] Katz NP, Gammaitoni AR, Davis MW, Dworkin RH and the Lidoderm Patch Study Group. Lidocaine patch 5% reduces pain intensity and interference with quality of life in patients with postherpetic neuralgia: an effectiveness trial. *Pain Med.* 2002;3(4):324-332.

Minimization of Risk

In addition to omitting important risk information, the direct mailing pieces also misleadingly minimize the risks they do mention.

First, one of the pieces (LD-1204F) minimizes Lidoderm's risks by virtue of its physical configuration. In this piece, all of the risk information is only accessible after pulling a tab on the front of the piece and then turning the page over and reading the back of the tab. If the tab is reinserted prior to turning the page, this information is no longer visible. There are also no signals within the piece to alert readers to the presence of this important risk information inside the tab.

Second, the information relating to risk that is presented in the pieces does not adequately describe the risks associated with Lidoderm. Specifically, the pieces claim: "Most commonly reported adverse event in this study was localized rash, which was considered to be related to study treatment in majority of cases" (LD-1204F) and "Most commonly reported adverse event was localized rash (12%)" (LD-1316B). These statements are insufficient to describe the myriad of application site reactions associated with Lidoderm use, as presented in the PI.

Communication of Indication

Both direct mailing pieces claim that Lidoderm is for "the neuropathic pain of postherpetic neuralgia (PHN)." This presentation is misleading because it fails to communicate an important limitation in Lidoderm's approved indication as reflected in the PI; specifically, that Lidoderm "…should be applied only to **intact skin.**" (emphasis in original). By failing to adequately communicate Lidoderm's approved indication, the direct mailing pieces fail to appropriately caution against unsafe use of Lidoderm, including application to broken or inflamed skin, which, according to the PRECAUTIONS section of the PI, "…may result in higher blood concentrations of lidocaine from increased absorption."

Conclusion and Requested Action

For the reasons discussed above, the direct mailing pieces are false or misleading because they make unsubstantiated effectiveness claims for Lidoderm, they omit and minimize serious risk information associated with use of the drug, and they inadequately communicate an important limitation in Lidoderm's approved indication. Accordingly, the pieces misbrand Lidoderm under 21 U.S.C. 352(a) and 321(n).

DDMAC requests that Endo immediately cease the dissemination of violative promotional materials for Lidoderm such as those described above. Please submit a written response to this letter on or before July 13, 2005 stating whether you intend to comply with this request, listing all violative promotional materials for Lidoderm such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, Maryland 20857, facsimile at 301-594-6771. In all future correspondence regarding this matter, please refer to MACMIS # 13494 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 Lidoderm comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas Abrams, RPh, MBA
Director
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/

Barbara Chong
6/28/05 04:38:40 PM
Signed for Thomas Abrams