DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Stacy Holdsworth, Pharm.D.
Manager
U.S. Regulatory Affairs
Eli Lilly and Company
Lilly Technology Center
Indianapolis, IN 46221

Re: NDA # 21-427, 21-733
Cymbalta® (duloxetine hydrochloride) Delayed-release Capsules
MACMIS # 13637

Dear Dr. Holdsworth:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed two professional journal ads (DD33650 and DD33979) for Cymbalta® (duloxetine hydrochloride) Delayed-release Capsules submitted by Eli Lilly and Company (Lilly) under cover of Form FDA 2253. DDMAC has concluded that the journal ads are false or misleading because they omit material facts essential to the safe and effective use of Cymbalta and, therefore, misbrand the drug in violation of section 502(n) of the Federal Food, Drug, and Cosmetic Act (Act) (21 U.S.C. § 352(n)) and FDA's implementing regulations. 21 CFR 202.1(e). See also section 201(n) of the Act, 21 U.S.C. § 321(n).

Background

Cymbalta is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI). According to its FDA-approved product labeling (PI), Cymbalta is approved for the following indications:

> ***Major Depressive Disorder***— Cymbalta is indicated for the treatment of major depressive disorder (MDD).
>
> The efficacy of Cymbalta has been established in 8- and 9-week placebo-controlled trials of outpatients who met DSM-IV diagnostic criteria for major depressive disorder (*see* CLINICAL STUDIES).
>
> A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or a suicide attempt or suicidal ideation.

The effectiveness of Cymbalta in hospitalized patients with major depressive disorder has not been studied.

The effectiveness of Cymbalta in long-term use for major depressive disorder, that is, for more than 9 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use Cymbalta for extended periods should periodically evaluate the long-term usefulness of the drug for the individual patient.

Diabetic Peripheral Neuropathic Pain— Cymbalta is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy (*see* CLINICAL STUDIES).

As stated in the PI approved at the time of dissemination of the violative journal ads,[1] Cymbalta is associated with numerous serious risks, including the following (in pertinent part):

CONTRAINDICATIONS

Hypersensitivity— Cymbalta is contraindicated in patients with a known hypersensitivity to duloxetine or any of the inactive ingredients.

Monoamine Oxidase Inhibitors— Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (*see* WARNINGS).

Uncontrolled Narrow-Angle Glaucoma— In clinical trials, Cymbalta use was associated with an increased risk of mydriasis; therefore, its use should be avoided in patients with uncontrolled narrow-angle glaucoma.

WARNINGS

Clinical Worsening and Suicide Risk — Patients with major depressive disorder, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs.…**Nevertheless, patients being treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases….**

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers….

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[1]The violative ads were initially disseminated in November 2004, prior to the most recent labeling revision.

> **Monoamine Oxidase Inhibitors (MAOI) — In patients receiving a serotonin reuptake inhibitor in combination with a monoamine oxidase inhibitor, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma…. Therefore, because Cymbalta is an inhibitor of both serotonin and norepinephrine reuptake, it is recommended that Cymbalta not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of Cymbalta, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI.**

(emphasis in original).

Misleading Product Claim Ad

The journal ads in question are product-specific prescription drug ads for Cymbalta. Although the name of the product is not mentioned in the main part of the ads, each ad includes a brief summary for Cymbalta, which mentions the name of the drug, its indications for use, and its dosage recommendations.

In addition, the ads also specifically promote Cymbalta in the following ways:

1. by describing a hypothesized mechanism of action in the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) and treatment of major depressive disorder (MDD), which is consistent with Cymbalta's PI. Cymbalta is the only drug approved for both management of neuropathic pain associated with DPN and treatment of MDD.; and

2. by claiming, "Diabetic peripheral neuropathic pain. When it's this painful, treating it shouldn't be. Enhancing serotonin and norepinephrine may offer relief." At the time of initial dissemination of the violative ads, Cymbalta was the only drug approved for the management of neuropathic pain associated with DPN and is hypothesized to potentiate serotonergic and noradrenergic activity in the CNS.

These product ads are misleading because they fail to reveal, in the main parts of the ads, material facts in light of the representations made or with respect to consequences that may result from the use of a product. Cymbalta is associated with several important risks as noted above, but the ads fail to disclose <u>any</u> of these risks within the main parts of the ads.

Conclusion and Requested Action

The journal ads are product claim ads for Cymbalta that omit material facts related to the indications and risks associated with the drug. Accordingly, the journal ads violate section 502(n) of the Act, 21 U.S.C. § 352(n), and FDA's implementing regulations (21 CFR 202.1(e)) and misbrand Cymbalta. See also section 201(n) of the Act, 21 U.S.C. § 321(n).

DDMAC requests that Lilly immediately cease the dissemination of promotional materials for Cymbalta that contain claims that are the same as or similar to those described above. Please submit a written response to this letter on or before September 23, 2005 describing your intent to comply with this request, listing all promotional materials for Cymbalta that contain claims that are the same as or similar to those described above, and explaining your plan for discontinuing use of these materials. Please direct your response to Michelle Safarik, MSPAS, PA-C 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 20705, facsimile at 301-796-9878. In all future correspondence regarding this matter, please refer to MACMIS ID # 13637 in addition to the NDA numbers. 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 Cymbalta comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Michelle Safarik, MSPAS, PA-C
Jialynn Wang, Pharm.D.
LT, USPHS
Regulatory Review Officers
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/

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