DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

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

Re: NDA # 21-733
CYMBALTA® (duloxetine hydrochloride) Delayed-release Capsules
MACMIS # 14550

Dear Dr. Sharp:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a professional mailer (mailer) (DD38459) for CYMBALTA® (duloxetine hydrochloride) Delayed-release Capsules (Cymbalta) submitted by Eli Lilly and Company (Lilly) under cover of Form FDA-2253. This mailer is false or misleading in that it overstates the efficacy of Cymbalta and omits some of the most serious and important risk information associated with its use. Therefore, the mailer misbrands the drug in violation of Sections 502(a) and 201(n) of the Federal Food, Drug and Cosmetic Act (Act), 21 U.S.C. 352(a) and 321(n), and FDA implementing regulations. Cf. 21 CFR 202.1(e)(3)(i) & (e)(5)(iii).

Background

According to its FDA-approved product labeling (PI), Cymbalta has three indications: the first is for the treatment of major depressive disorder; the second is for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN); and the third is for the treatment of generalized anxiety disorder. In the mailer, the drug is being recommended or suggested for only the second indication, the management of neuropathic pain associated with DPN.

The PI for Cymbalta contains the following Boxed Warning discussing suicidality and antidepressant drugs:

WARNING

Suicidality and Antidepressant Drugs – Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Cymbalta or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults

aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Cymbalta is not approved for use in pediatric patients. (*See* WARNINGS, Clinical Worsening and Suicide Risk, PRECAUTIONS, Information for Patients, PRECAUTIONS, Pediatric Use.)

The PI also states that Cymbalta is associated with other serious and important risks, including the following (in pertinent part):

CONTRAINDICATIONS

. . . .

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

. . . .

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.
. . . .

PRECAUTIONS

General
Hepatotoxicity – Cymbalta increases the risk of elevation of serum transaminase levels. Liver transaminase elevations resulted in the discontinuation of 0.4% (31/8454) of Cymbalta-treated patients. In these patients, the median time to detection of the transaminase elevation was

about two months. . . . In controlled trials in DPN, elevations of ALT to >3 times the upper limit of normal occurred in 1.68% (8/477) of Cymbalta-treated patients and in 0% (0/187) of placebo-treated patients. . . . Postmarketing reports have described cases of hepatitis with abdominal pain, hepatomegaly and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. . . . [C]ymbalta should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

. . . .

Discontinuation of Treatment with Cymbalta - Discontinuation symptoms have been systematically evaluated in patients taking duloxetine.

. . . .

A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible.

. . . .

Use in Patients with Concomitant Illness – Clinical experience with Cymbalta in patients with concomitant systemic illnesses is limited. There is no information on the effect that alterations in gastric motility may have on the stability of Cymbalta's enteric coating. As duloxetine is rapidly hydrolyzed in acidic media to naphthol, caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (e.g., some diabetics).

. . . .

[C]ymbalta is not recommended for patients with end-stage renal disease or severe renal impairment. . . . Markedly increased exposure to duloxetine occurs in patients with hepatic insufficiency and Cymbalta should not be administered to these patients.

(emphasis original)

Overstatement of Efficacy

The first inside flap of the mailer contains the header "Effective" with the following superimposed claim, "In pooled clinical trials, patients with diabetic peripheral neuropathic pain (DPNP) experienced significantly less pain interference with overall functioning using Cymbalta 60 or 120 mg/day.[1]" Beneath this claim is a graph entitled, "**Pain interference on patient overall functioning**" (emphasis original) that presents percent change from baseline in the individual items, as well as the average score, of the Brief Pain Inventory – Interference Portion (BPI) Score in patients treated with Cymbalta 60 mg/day, Cymbalta 120 mg/day, or placebo. The graph shows patient response with respect to the following parameters: BPI Average Score; General Activity; Mood; Walking Ability; Normal Work; Relationships with Others; Sleep; and Enjoyment of Life, claiming nominally significant results for

[1] Data on file, Lilly Research Laboratories: CYM20050314F

each item. On the next flap, the mailer includes the claim, "*Help your DPNP patients experience less pain interference with overall functioning*." (emphasis original)

These claims and presentations are false or misleading because they overstate the efficacy of Cymbalta by suggesting that patients with DPN who are treated with the drug experience significantly less pain interference with overall functioning, when this has not been demonstrated by substantial evidence or substantial clinical experience.

The reference cited[1] to support the claim, "significantly less pain interference with overall functioning" with Cymbalta treatment does not constitute substantial evidence because it reports pooled efficacy data from multiple studies that were submitted to the new drug application (NDA) to support the BPI findings. The submitted studies of effects on the BPI pain interference subscale failed to demonstrate a statistically significant separation from placebo in the individual efficacy studies submitted to the NDA. Pooling the data can yield a statistically significant difference, but this post-hoc analysis is not a credible source of data. A claimed effect on the BPI-Interference Portion needs to be supported by a prospectively planned analysis of a study designed to test this effect. Generally, findings measured by instruments that measure patient-reported outcomes may be used to support claims if the claims are derived from adequate and well-controlled investigations that use patient-reported outcome instruments that reliably and validly measure the specific concepts at issue.

Moreover, the studies at issue were not adequately designed to substantiate the claim of "significantly less pain interference with overall functioning." The reference cited[1] contains the BPI, which purportedly assesses two main factors: "pain intensity" and "pain interference" (in the patient's life). The graph described above reflects data for the "pain interference" subscale of the BPI. We acknowledge that the BPI asks patients to rate their level of pain interference using the seven items depicted in the chart described above (general activity; mood; walking ability; normal work; relationships with others; sleep; and enjoyment of life). However, each of the seven items in the BPI pain interference subscale measures a general concept that cannot be adequately captured with a single-item question.[2] For example, for each question, patients are required to rate pain interference as it pertains to each of these general concepts by averaging their experience across all important aspects of that general concept. We do not know of any evidence that patient responses to such questions yield valid data. In addition, each pain interference question requires patients to compare their current condition to a previous state without pain. Again, we do not know of any evidence that patient responses to questions like these yield valid data. Consequently, we do not believe there is evidence that their responses are valid or reliable.

Thus, apart from problems related to unplanned, post-facto pooling of data, we do not believe the subscale used has been validated. The pooled studies cannot provide substantial evidence to support the claims implied by the individual items or even the overall claim, "significantly less pain interference with overall functioning." 21 CFR 314.126(b)(6).

---

[2] Generally, when the concept of interest is general, for example, physical function, a single-item question usually is unable to provide a complete understanding of the treatment's effect because a single item cannot capture all the domains of the general concept.

Omission of Material Facts

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. Although the mailer presents numerous efficacy claims, it fails to communicate some of the most serious risks associated with the use of Cymbalta. While the mailer does include some information from the Boxed Warning and the Adverse Reactions sections of the PI, it fails to include other important risk information. More specifically, it fails to reveal the Contraindication regarding use in patients with uncontrolled narrow-angle glaucoma and the Contraindication and bolded Warning relating to use with monoamine oxidase inhibitors (see Background section). Furthermore, the mailer fails to reveal the Precautions relating to hepatotoxicity, abrupt discontinuation of Cymbalta treatment, and use of the drug in patients with concomitant illness. The fact that the mailer contains the statement, "**See additional Important Safety Information and full Prescribing Information, including Boxed Warning, inside this mailer.**" (emphasis original) on its middle flap and that a removable PI is located in its interior pocket does not mitigate these misleading omissions.

Conclusion and Requested Action

For the reasons discussed above, the mailer misbrands Cymbalta in violation of the Act, 21 U.S.C. 352(a) and 321(n), FDA implementing regulations. Cf. 21 CFR 202.1(e)(3)(i) & (e)(5)(iii).

DDMAC requests that Lilly immediately cease the dissemination of promotional materials for Cymbalta the same as or similar to those described above. To that end, we note there are similar claims and presentations for Cymbalta in several other promotional materials submitted under cover of Form FDA-2253, including the Cymbalta Sales Aid (DD47150), Cymbalta Endo Speaker Slide Kit (DD47228), Cymbalta PODS Module 2 Endo (DD45976), Cymbalta Sell Sheet (DD47050), and Cymbalta Regional Congress Table Top Panels (DD46213). Please submit a written response to this letter on or before October 5, 2007, stating whether you intend 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 me 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 20705-1266, or by facsimile at 301-796-9877. In all future correspondence regarding this matter, please refer to MACMIS ID # 14550 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 Cymbalta comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Michelle Safarik, MSPAS, PA-C
Regulatory Review Officer
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/

Michelle Safarik

9/21/2007 01:18:30 PM