Dear Healthcare Professional,

At MPR we strive to bring you important drug information in a timely fashion. In keeping with this goal, we are pleased to bring you this CLINICAL ALERT emphasizing the safety and efficacy of Cymbalta® (duloxetine HCl) 20 mg, 30 mg, and 60 mg Delayed-Release Capsules, manufactured by Eli Lilly and Company, in the treatment of generalized anxiety disorder (GAD).¹

The efficacy of Cymbalta for the treatment of GAD was established in 3 short-term trials and 1 maintenance trial in adults, all of which showed significant change on the Hamilton Anxiety Rating Scale Total Score (the primary endpoint).²⁻⁵

Common adverse events leading to treatment discontinuation in GAD trials included nausea (3.7% vs 0.2%), vomiting (1.3% vs 0.0%), and dizziness (1.0% vs 0.2%) with Cymbalta versus placebo, respectively.¹

Please remember that Cymbalta, like all SSRIs and SNRIs, has a Boxed Warning for suicidality:

- Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children, adolescents, and young adults with major depressive disorder (MDD) and other psychiatric disorders.
- Patients of all ages started on therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior.
- Cymbalta is not approved for use in pediatric patients.

More information about Cymbalta is available in the current edition of MPR.

Sincerely,

Grace L. McBride
Editorial Director
MPR Custom Programs

Please see Important Safety Information, including Boxed Warning, on pages 2 to 4; Prescribing Information; and Medication Guide.

(Important Safety Information on next page)
Important Safety Information About Cymbalta

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.

Contraindications

• Concomitant use in patients taking Monoamine Oxidase Inhibitors (MAOIs) is contraindicated due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs. These interactions may include 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. These reactions have also been reported in patients who have recently discontinued serotonin reuptake inhibitors and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Cymbalta. In addition, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI.

• Cymbalta was associated with an increased risk of mydriasis; therefore, it should not be used in patients with uncontrolled narrow-angle glaucoma and used cautiously in patients with controlled narrow-angle glaucoma.

Warnings and Precautions

• Clinical Worsening and Suicide Risk

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially within the first few months of treatment and when changing the dose. Consider changing the therapeutic regimen, including possibly discontinuing the medication in patients whose depression is persistently worse or includes symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, or suicidality that are severe, abrupt in onset, or were not part of the patient’s presenting symptoms. If discontinuing treatment, the medication should be tapered. Families and caregivers of patients being treated with antidepressants for any indication should be alerted about the need to monitor patients. Prescriptions for Cymbalta should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

• Hepatic failure, sometimes fatal, has been reported in patients treated with Cymbalta. Cymbalta should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established.

(Important Safety Information continued on next page)
• Because it is possible that Cymbalta and alcohol may interact to cause liver injury or that Cymbalta may aggravate pre-existing liver disease, Cymbalta should not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

• Orthostatic hypotension and syncope have been reported with therapeutic doses of Cymbalta. This tends to occur within the first week of therapy but can occur at any time during Cymbalta treatment, particularly after dose increases. Consideration should be given to discontinuing Cymbalta in patients who experience symptomatic orthostatic hypotension and/or syncope.

• The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs alone, including Cymbalta treatment, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms. Concomitant use with serotonin precursors (e.g., tryptophan) is not recommended. Treatment with duloxetine and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

• SSRIs and SNRIs, including Cymbalta, may increase the risk of bleeding events. Patients should be cautioned about the risk of bleeding associated with concomitant use of Cymbalta and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation.

• On abrupt or tapered discontinuation, spontaneous reports of adverse events, some of which may be serious, have been reported during the marketing of SSRIs and SNRIs. A gradual reduction in dose rather than abrupt cessation is recommended when possible.

• Cymbalta should be used cautiously in patients with a history of mania or with a history of a seizure disorder.

• In clinical trials across indications relative to placebo, treatment with Cymbalta was associated with mean increases of 0.5 mm Hg in systolic blood pressure and 0.8 mm Hg in diastolic blood pressure compared to mean decreases of 0.6 mm Hg systolic and 0.4 mm Hg diastolic in placebo-treated patients. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment.

• Co-administration of Cymbalta with potent CYP1A2 inhibitors or thioridazine should be avoided.

• SSRIs and SNRIs, including Cymbalta, have been associated with cases of clinically significant hyponatremia that appeared to be reversible when Cymbalta was discontinued. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs.

• The effect that alterations in gastric motility may have on the stability of the enteric coating of Cymbalta is unknown. 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).

(Important Safety Information continued on next page)
Warnings and Precautions (Cont.)

- Cymbalta should ordinarily not be administered to patients with any hepatic insufficiency or patients with end-stage renal disease (requiring dialysis) or severe renal impairment (creatinine clearance <30 mL/min).
- As observed in DPNP trials, Cymbalta treatment worsens glycemic control in some patients with diabetes. In the extension phases (up to 52 weeks) of the DPNP studies, an increase in HbA1c in both the Cymbalta (0.5%) and the routine care groups (0.2%) was noted.
- Cymbalta is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during Cymbalta treatment, this effect may be drug-related. In postmarketing experience, urinary retention has been observed.

Use in Specific Populations

- Pregnancy and Nursing Mothers: Use only if the potential benefit justifies the potential risk to the fetus or child.

Most Common Adverse Events

- The most commonly reported adverse events (≥5% and at least twice placebo) for Cymbalta vs placebo in controlled clinical trials (N=6020 vs 3962) were: nausea (24% vs 8%), dry mouth (13% vs 5%), somnolence* (10% vs 3%), fatigue (10% vs 5%), constipation* (10% vs 4%), dizziness (10% vs 5%), decreased appetite* (8% vs 2%), and increased sweating (7% vs 2%).

*Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies that did not have a placebo lead-in period or dose titration.

- In placebo-controlled clinical trials, the overall discontinuation rates due to adverse events were:
  MDD: 9% vs 5%; GAD: 15% vs 4%; DPNP: 13% vs 5%; FM: 20% vs 12%; OA: 16% vs 6%; CLBP: 17% vs 6%.

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See Prescribing Information, including Boxed Warning, and Medication Guide.

REFERENCES

Company: Eli Lilly and Company  
Pharmacologic Class: Serotonin and norepinephrine reuptake inhibitor  
Indications: Treatment of generalized anxiety disorder (GAD); efficacy was established in three short-term trials and one maintenance trial in adults.  
Dosing: GAD: 60 mg/day (once daily); may start at 30 mg/day for 1 week before increasing dose to 60 mg.  
How Supplied: Caps (20 mg) — 60; (30 mg) — 30, 90, 100 (UD), 1000; (60 mg) — 30, 100 (UD), 1000

Efficacy of Cymbalta was established in 4 acute, general anxiety disorder (GAD) clinical trials (Figure 1).1-4

Figure 1

Select Important Safety Information About Cymbalta

- Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children, adolescents, and young adults with major depressive disorder (MDD) and other psychiatric disorders.
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During GAD clinical trials, the dose of Cymbalta ranged from 60 mg to 120 mg per day

- While a 120 mg/day dose was shown to be effective, there is no evidence that doses greater than 60 mg/day confer additional benefit.

**Results of Cymbalta treatment in patients with GAD**

- Cymbalta 60 mg/day and 120 mg/day demonstrated superiority over placebo, measured by greater improvement in the HAM-A Total Score (Figure 2).  
  - Significant reduction in GAD symptoms was reported as early as week 2 of treatment with Cymbalta 60 mg/day and 120 mg/day.

- Cymbalta improved patient functioning as measured by the Sheehan Disability Scale (SDS) in the acute GAD trials.
  - SDS Global Functional Impairment Score measures the extent emotional symptoms disrupt patient functioning in 3 life domains: work/school, social life/leisure activities, and family life/home responsibilities.

**Figure 2**

**Cymbalta demonstrated superiority over placebo as measured by greater improvement in the HAM-A Total Score**

<table>
<thead>
<tr>
<th>Weeks on Study Drug</th>
<th>Mean Change from Baseline (HAM-A Total Score)</th>
</tr>
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<tbody>
<tr>
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</tr>
<tr>
<td>1</td>
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<td>8</td>
<td>+5</td>
</tr>
<tr>
<td>9</td>
<td>+5.5</td>
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*Ps ≤ 0.001 Cymbalta vs placebo by MMRM

Results of one outpatient study, which had a mean Hamilton Anxiety Rating Scale (HAM-A) Total Score of ~25-26 out of 56 at baseline. HAM-A Total Score was the primary endpoint in all 4 studies.

MMRM=Mixed-effects Model Repeated Measures analysis.

Sources: Koponen et al, 2007; Data on file, CYM20090505F.

**Improvement with Cymbalta was observed throughout the acute GAD trials**

- Significant changes in HAM-A Total Score (the primary endpoint) for Cymbalta 60 mg to 120 mg per day vs placebo have been replicated in 3 acute clinical trials.

Select Important Safety Information About Cymbalta (duloxetine HCl)

**Contraindications**

- Use of a Monoamine Oxidase Inhibitor concomitantly or in close temporal proximity.

- Not for use in patients with uncontrolled narrow-angle glaucoma.

Please see Important Safety Information, including Boxed Warning, on pages 2 to 4; Prescribing Information; and Medication Guide.
Reduced estimated probability of GAD relapse

- Relapse prevention study consisted of a 26-week, open-label, flexible dose acute therapy phase followed by a 26-week, double-blind, placebo-controlled continuation therapy phase.
- The following criteria needed to be met:
  - Decrease from baseline HAM-A Total Score by ≥50% to a score of ≤11
  - Clinical Global Impression-Improvement (CGI-I) score of 1 or 2
- Patients treated with Cymbalta had an estimated probability of relapse of 15% compared to 46% for patients who switched to placebo ($P \leq 0.05$) (Figure 3).

Figure 3

**ESTIMATED PROBABILITY OF RELAPSE IN A MAINTENANCE GENERALIZED ANXIETY DISORDER CLINICAL TRIAL**

The primary efficacy measure was the time to relapse during the 26-week, double-blind continuation therapy phase. Relapse was defined as an increase in the CGI-S rating of at least 2 points from randomization (end of open-label phase) to a score of ≥4 (moderate) while meeting criteria for GAD confirmed by the MINI or by discontinuation due to lack of efficacy.

Sources: Davidson et al, 2008; Data on file, CYM20091207A.

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**Warnings and Precautions**

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REFERENCES

5. Data on file, Lilly Research Laboratories: CYM20090505F.  