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Re: Safety data on Cymbalta® (duloxetine hydrochloride) – Hepatic Effects

Dear Health Care Professional,

Eli Lilly and Company would like to inform you of new safety information regarding hepatotoxicity with Cymbalta® (duloxetine hydrochloride). This information comes from postmarketing reports of hepatic injury (including hepatitis and cholestatic jaundice). Some of these reports indicate that patients with preexisting liver disease who take duloxetine may have an increased risk for further liver damage. The new labeling extends the Precaution against using Cymbalta in patients with substantial alcohol use to include those patients with chronic liver disease.

The following is updated language in the PRECAUTIONS of the Cymbalta package insert, and will be reflected in other materials. The language that has been added is underlined. Language that was deleted is shown in ~~strikethrough~~.

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 MDD, elevations of alanine transaminase (ALT) to >3 times the upper limit of normal occurred in 0.9% (8/930) of Cymbalta-treated patients and in 0.3% (2/652) of placebo-treated patients. 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. In the full cohort of placebo-controlled trials in any indication, 1% (39/3732) of Cymbalta-treated patients had a >3 times the upper limit of normal elevation of ALT compared to 0.2% (6/2568) of placebo-treated patients. In placebo-controlled studies using a fixed-dose design, there was evidence of a dose-response relationship for ALT and AST elevation of >3 times the upper limit of normal and >5 times the upper limit of normal, respectively. 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. Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported.
The combination of transaminase elevations and elevated bilirubin, without evidence of obstruction, is generally recognized as an important predictor of severe liver injury. In clinical trials, three Cymbalta patients had elevations of transaminases and bilirubin, but also had elevation of alkaline phosphatase, suggesting an obstructive process; in these patients, there was evidence of heavy alcohol use and this may have contributed to the abnormalities seen. Two placebo-treated patients also had transaminase elevations with elevated bilirubin. ~~Severe elevations of liver enzymes (>10 times the upper limit of normal) or liver injury with a cholestatic or mixed pattern have been rarely reported, in some cases associated with excessive alcohol use.~~ Postmarketing reports indicate that elevated transaminases, bilirubin and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis. Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Prior to approval, and as described in PRECAUTIONS of the previous package insert, it was known that use of duloxetine was associated with mild to moderate and usually transient elevation of hepatic enzymes that infrequently led to Cymbalta discontinuation. In addition, some cases of severe hepatic injury in patients consuming large quantities of alcohol were observed during duloxetine clinical trials, as is described in the original package insert.

Since approval on August 3, 2004, approximately one million patients have taken duloxetine. Among these, several cases of hepatic injury have been spontaneously reported. Some of these patients had underlying liver disease. Review of these cases suggests that patients with underlying chronic liver disease may be at increased risk of hepatotoxicity with duloxetine. In addition to hepatocellular and mixed liver injury, cases of cholestatic jaundice have been reported.

Patients and prescribers should be aware of the signs and symptoms of liver damage (pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained "flu-like" symptoms) and health care professionals are encouraged to investigate such symptoms and signs promptly.

Should you have any questions or concerns regarding this important safety information, please contact your Eli Lilly and Company sales representative or contact the Lilly medical department at 1-800-Lilly-Rx. Please refer to the full prescribing information for Cymbalta included with this letter. As always, we request that serious adverse events be reported to Lilly at 1-800-Lilly-Rx or to the FDA MedWatch program by phone (1-800-FDA-1088), by fax (1-800-FDA-0178) or by email (www.fda.gov/medwatch).

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Eli Lilly and Company