

Anti-TNF Agents Curb Ankylosing Spondylitis

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CANCÚN, MEXICO – Most ankylosing spondylitis patients who have elevated disease activity and inflammatory back pain that is not controlled with conventional therapy have been shown to respond to anti-tumor necrosis factor

therapy, according to findings from a recent study.

Importantly, “disease activity will most likely not result in improvement,” Dr. Nathan Vastesaegeer reported at the meeting. As such, “the treating physician should consider a defined trial period with a TNF inhibitor if disease activity is not controlled with conventional therapy,” he said.

Specifically, patient age, peripheral en-

thesitis measure, C-reactive protein (CRP) level, functionality, and human leukocyte antigen B27 (HLA-B27) genotype are also associated with the likelihood that a patient with ankylosing spondylitis (AS) will respond to anti-TNF, reported Dr. Vastesaegeer.

The findings are based on analysis of data, separately and combined, from two randomized controlled trials to model the probability of achieving response or

remission after initiating anti-TNF therapy or continuing conventional therapy with NSAIDs, disease-modifying antirheumatic drugs (DMARDs), or steroids for AS, said Dr. Vastesaegeer of Schering-Plough.

The two studies included in the analysis were the ASSERT (Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy) trial and the GO-RAISE (Golimumab – A

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.

The concomitant use of Cymbalta with MAOIs intended to treat depression is contraindicated [see Contraindications].

If concomitant treatment of Cymbalta with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases [see Drug Interactions].

The concomitant use of Cymbalta with serotonin precursors (such as tryptophan) is not recommended [see Drug Interactions].

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.

Abnormal Bleeding—SSRIs and SNRIs, including duloxetine, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anti-coagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRI and SNRI use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of duloxetine and NSAIDs, aspirin, or other drugs that affect coagulation.

Discontinuation of Treatment with Cymbalta—Discontinuation symptoms have been systematically evaluated in patients taking duloxetine. Following abrupt or tapered discontinuation in placebo-controlled clinical trials, the following symptoms occurred at 1% or greater and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness, nausea, headache, paresthesia, fatigue, vomiting, irritability, insomnia, diarrhea, anxiety, and hyperhidrosis.

During marketing of other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe.

Patients should be monitored for these symptoms when discontinuing treatment with Cymbalta. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate [see Dosage and Administration].

Activation of Mania/Hypomania—In placebo-controlled trials in patients with major depressive disorder, activation of mania or hypomania was reported in 0.1% (2/2489) of duloxetine-treated patients and 0.1% (1/1625) of placebo-treated patients. No activation of mania or hypomania was reported in GAD, fibromyalgia, or chronic musculoskeletal pain placebo-controlled trials. Activation of mania or hypomania has been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs effective in the treatment of major depressive disorder. As with these other agents, Cymbalta should be used cautiously in patients with a history of mania.

Seizures—Duloxetine has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. In placebo-controlled clinical trials, seizures/convulsions occurred in 0.03% (3/10,524) of patients treated with duloxetine and 0.01% (1/7699) of patients treated with placebo. Cymbalta should be prescribed with care in patients with a history of a seizure disorder.

Effect on Blood Pressure—In placebo-controlled clinical trials across indications from baseline to endpoint, duloxetine treatment 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. In a clinical pharmacology study designed to evaluate the effects of duloxetine on various parameters, including blood pressure at supratherapeutic doses with an accelerated dose titration, there was evidence of increases in supine blood pressure at doses up to 200 mg twice daily. At the highest 200 mg twice daily dose, the increase in mean pulse rate was 5.0 to 6.8 beats and increases in mean blood pressure were 4.7 to 6.8 mm Hg (systolic) and 4.5 to 7 mm Hg (diastolic) up to 12 hours after dosing.

Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment [see Adverse Reactions].

Clinically Important Drug Interactions—Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Potential for Other Drugs to Affect Cymbalta

CYP1A2 Inhibitors—Co-administration of Cymbalta with potent CYP1A2 inhibitors should be avoided [see Drug Interactions].

CYP2D6 Inhibitors—Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 would be expected to, and does, result in higher concentrations (on average of 60%) of duloxetine [see Drug Interactions].

Potential for Cymbalta to Affect Other Drugs

Drugs Metabolized by CYP2D6—Co-administration of Cymbalta with drugs that are extensively metabolized by CYP2D6 and that have a narrow therapeutic index, including certain antidepressants (tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), phenothiazines, and Type 1C antiarrhythmics (e.g., propafenone, flecainide), and should be approached with caution. Plasma TCA concentrations may need to be monitored and the dose of the TCA may need to be reduced if a TCA is co-administered with Cymbalta. Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, Cymbalta and thioridazine should not be co-administered [see Drug Interactions].

Other Clinically Important Drug Interactions

Alcohol—Use of Cymbalta concomitantly with heavy alcohol intake may be associated with severe liver injury. For this reason, Cymbalta should not be prescribed for patients with substantial alcohol use [see Warnings and Precautions and Drug Interactions].

CNS Acting Drugs—Given the primary CNS effects of Cymbalta, it should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action [see Warnings and Precautions and Drug Interactions].

Hyponatremia—Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Cymbalta. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported and appeared to be reversible when Cymbalta was discontinued. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk [see Use in Specific Populations]. Discontinuation of Cymbalta should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. More severe and/or acute cases have been associated with hallucination, syncope, seizure, coma, respiratory arrest, and death.

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. In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (e.g., some diabetics).

Cymbalta has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable coronary artery disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing.

Hepatic Insufficiency—Cymbalta should ordinarily not be used in patients with hepatic insufficiency [see Warnings and Precautions and Use in Specific Populations].

Severe Renal Impairment—Cymbalta should ordinarily not be used in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min). Increased plasma concentration of duloxetine, and especially of its metabolites, occur in patients with end-stage renal disease (requiring dialysis) [see Use in Specific Populations].

Controlled Narrow-Angle Glaucoma—In clinical trials, Cymbalta was associated with an increased risk of mydriasis; therefore, it should be used cautiously in patients with controlled narrow-angle glaucoma [see Contraindications].

Glycemic Control in Patients with Diabetes—As observed in DPNP trials, Cymbalta treatment worsens glycemic control in some patients with diabetes. In three clinical trials of Cymbalta for the management of neuropathic pain associated with diabetic peripheral neuropathy, the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 176 mg/dL, and the mean baseline hemoglobin A_{1c} (HbA_{1c}) was 7.8%. In the 12-week acute treatment phase of these studies, Cymbalta was associated with a small increase in mean fasting blood glucose as compared to placebo. In the extension phase of these studies, which lasted up to 52 weeks, mean fasting blood glucose increased by 12 mg/dL in the Cymbalta group and decreased by 11.5 mg/dL in the routine care group. HbA_{1c} increased by 0.5% in the Cymbalta group and by 0.2% in the routine care groups.

Urinary Hesitation and Retention—Cymbalta is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during treatment with Cymbalta, consideration should be given to the possibility that they might be drug-related.

In postmarketing experience, cases of urinary retention have been observed. In some instances of urinary retention associated with duloxetine use, hospitalization and/or catheterization has been needed.

Laboratory Tests—No specific laboratory tests are recommended.

ADVERSE REACTIONS: Clinical Trial Data Sources—The data described below reflect exposure to duloxetine in placebo-controlled trials for MDD (N=2489), GAD (N=910), OA (N=239), CLBP (N=600), DPNP (N=906), and FM (N=876). The population studied was 17 to 91 years of age; 65.5%, 62.5%, 61.5%, 42.9%, and 94.9% female; and 86.5%, 81.2%, 86.2%, 74.0%, and 88% Caucasian for MDD, GAD, OA and CLBP, DPNP, and FM, respectively. Most patients received doses of a total of 60 to 120 mg per day [see Clinical Studies (14)].

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. Reactions reported during the studies were not necessarily caused by the therapy, and the frequencies do not reflect investigator impression (assessment) of causality.

Randomized Study in Ankylosing Spondylitis Subjects of a Novel Anti-TNF mAb Injection Given Every Four Weeks) trial.

The two studies combined comprised 479 AS patients treated with anti-TNF drugs and 156 AS patients treated with placebo and continued conventional therapy. All of the patients included in the analysis had Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores of at least 4 and spinal pain assessment scores of at least 4.

The prediction model incorporated patient age, enthesitis score, CRP level,

Bath AS Functional Index (BASFI) score, and HLA-B27 genotype. The mean age of the patients included in the analysis was 39.5 years, and the mean BASFI, CRP, and enthesitis measures were 5.4, 2.1, and 2.4, respectively.

For the ASSERT, GO-RAISE, and combined data, the area under the ROC curve for 50% improvement in BASDAI score (BASDAI50) at 12 weeks was 82%, 75%, and 77%, respectively, and for Assessment in AS (ASAS) partial remission at 24 weeks was 80%, 77%, and 78%, reported Dr. Vastesaeger. When the data were categorized by age (40 years or

younger vs. older than 40 years), enthesitis score (0 vs. greater than 0), CRP level (0.6 mg/dL or less, greater than 0.6-2 mg/dL, and greater than 2 mg/dL), and BASFI score (4.5 or less, greater than 4.5-6.5, and greater than 6.5), “the area under the curve of the combined data set prediction model was 80% for [BASDAI50] response and 77% for [ASAS] partial remission,” he reported. “This suggests a good prediction model according to the academic point system.”

In a matrix model designed to represent increasing proportion of BASDAI50 response and ASAS partial remission

with respect to baseline characteristics, “only 2% of patients who did not have BASDAI50 response at week 12 had ASAS partial remission at week 24,” said Dr. Vastesaeger.

The development of the matrix model was reported by Dr. Vastesaeger and his coinvestigators in *Annals of the Rheumatic Diseases* (Ann. Rheum. Dis. 2011 March 14 [doi:10.1136/ard.2010.147744]).

Dr. Vastesaeger is an employee of Schering-Plough. He reported having no conflicts of interest with respect to this presentation. ■

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials—Major Depressive Disorder—Approximately 9% (209/2327) of the patients who received duloxetine in placebo-controlled trials for MDD discontinued treatment due to an adverse reaction, compared with 4.7% (68/1460) of the patients receiving placebo. Nausea (duloxetine 1.3%, placebo 0.5%) was the only common adverse reaction reported as a reason for discontinuation and considered to be drug-related (i.e., discontinuation occurring in at least 1% of the duloxetine-treated patients and at a rate of at least twice that of placebo).

Generalized Anxiety Disorder—Approximately 15.3% (102/668) of the patients who received duloxetine in placebo-controlled trials for GAD discontinued treatment due to an adverse reaction, compared with 4.0% (20/495) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 3.7%, placebo 0.2%), and vomiting (duloxetine 1.3%, placebo 0.0%), and dizziness (duloxetine 1.0%, placebo 0.2%).

Diabetic Peripheral Neuropathic Pain—Approximately 12.9% (117/906) of the patients who received duloxetine in placebo-controlled trials for DPNP discontinued treatment due to an adverse reaction, compared with 5.1% (23/448) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 3.5%, placebo 0.7%), dizziness (duloxetine 1.2%, placebo 0.4%), and somnolence (duloxetine 1.1%, placebo 0.0%).

Fibromyalgia—Approximately 19.6% (172/876) of the patients who received duloxetine in 3- to 6-month placebo-controlled trials for FM discontinued treatment due to an adverse reaction, compared with 11.8% (63/535) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 1.9%, placebo 0.7%), somnolence (duloxetine 1.5%, placebo 0.0%), and fatigue (duloxetine 1.3%, placebo 0.2%).

Chronic Pain due to Osteoarthritis—Approximately 16.3% (39/239) of the patients who received duloxetine in 13-week, placebo-controlled trials for chronic pain due to OA discontinued treatment due to an adverse reaction, compared with 5.6% (14/248) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 2.9%, placebo 0.8%) and asthenia (duloxetine 1.3%, placebo 0.0%).

Chronic Low Back Pain—Approximately 16.5% (99/600) of the patients who received duloxetine in 13-week, placebo-controlled trials for CLBP discontinued treatment due to an adverse reaction, compared with 6.3% (28/441) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 3.0%, placebo 0.7%), and somnolence (duloxetine 1.0%, placebo 0.0%).

Most Common Adverse Reactions—Pooled Trials for all Approved Indications—The most commonly observed adverse reactions in Cymbalta-treated patients (incidence of at least 5% and at least twice the incidence in placebo patients) were nausea, dry mouth, somnolence, fatigue, constipation, decreased appetite, and hyperhidrosis.

Diabetic Peripheral Neuropathic Pain—The most commonly observed adverse reactions in Cymbalta-treated patients (as defined above) were nausea, somnolence, decreased appetite, constipation, hyperhidrosis, and dry mouth.

Fibromyalgia—The most commonly observed adverse reactions in Cymbalta-treated patients (as defined above) were nausea, dry mouth, constipation, somnolence, decreased appetite, hyperhidrosis, and agitation.

Chronic Pain due to Osteoarthritis—The most commonly observed adverse reactions in Cymbalta-treated patients (as defined above) were nausea, fatigue, and constipation.

Chronic Low Back Pain—The most commonly observed adverse reactions in Cymbalta-treated patients (as defined above) were nausea, dry mouth, insomnia, somnolence, constipation, dizziness, and fatigue.

Adverse Reactions Occurring at an Incidence of 5% or More Among Duloxetine-Treated Patients in Placebo-Controlled Trials—Table 2 in full PI gives the incidence of treatment-emergent adverse reactions in placebo-controlled trials (N=6020 Cymbalta; N=3962 placebo) for approved indications that occurred in 5% or more of patients treated with duloxetine and with an incidence greater than placebo. These adverse events were: nausea, headache, dry mouth, fatigue (includes asthenia), somnolence* (includes hypersomnia and sedation), insomnia* (includes middle insomnia, early morning awakening, and initial insomnia), dizziness, constipation*, diarrhea, decreased appetite* (includes anorexia), and hyperhidrosis.

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

Adverse Reactions Occurring at an Incidence of 2% or More Among Duloxetine-Treated Patients in Placebo-Controlled Trials—Pooled MDD and GAD Trials—Table 3 in full PI gives the incidence of treatment-emergent adverse reactions in MDD and GAD placebo-controlled trials (N=2995 Cymbalta; N=1955 placebo) for approved indications that occurred in 2% or more of patients treated with duloxetine and with an incidence greater than placebo. These adverse events were: **Cardiac Disorders**—palpitations; **Eye Disorders**—vision blurred; **Gastrointestinal Disorders**—nausea, dry mouth, diarrhea, constipation*, abdominal pain (includes abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort, and gastrointestinal pain), vomiting; **General Disorders and Administration Site Conditions**—fatigue (includes asthenia); **Investigations**—weight decreased*; **Metabolism and Nutrition Disorders**—decreased appetite (includes anorexia); **Nervous System Disorders**—dizziness, somnolence (includes hypersomnia and sedation), tremor; **Psychiatric Disorders**—

insomnia (includes middle insomnia, early morning awakening, and initial insomnia), agitation (includes feeling jittery, nervousness, restlessness, tension, and psychomotor agitation), anxiety, libido decreased (includes loss of libido), orgasm abnormal (includes anorgasmia), abnormal dreams (includes nightmare); **Reproductive System and Breast Disorders**—erectile dysfunction, ejaculation delayed*, ejaculation disorder (includes ejaculation failure and ejaculation dysfunction); **Respiratory, Thoracic, and Mediastinal Disorders**—yawning; **Skin and Subcutaneous Tissue Disorders**—hyperhidrosis; **Vascular Disorders**—hot flush.

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

DPNP, FM, OA, and CLBP—Table 4 in full PI gives the incidence of treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta (determined prior to rounding) in the premarketing acute phase of DPNP, FM, OA, and CLBP placebo-controlled trials (N=2621 Cymbalta; N=1672 placebo) and with an incidence greater than placebo. These adverse events were: **Gastrointestinal Disorders**—nausea, dry mouth*, constipation*, diarrhea, abdominal pain (includes abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, and gastrointestinal pain), vomiting, dyspepsia (includes stomach discomfort); **General Disorders and Administration Site Conditions**—fatigue (includes asthenia); **Infections and Infestations**—nasopharyngitis, upper respiratory tract infection, influenza; **Metabolism and Nutrition Disorders**—decreased appetite* (includes anorexia); **Musculoskeletal and Connective Tissue Disorders**—musculoskeletal pain* (includes myalgia and neck pain), muscle spasm; **Nervous System Disorders**—headache, somnolence* (includes hypersomnia and sedation), dizziness, paraesthesia (includes hypoaesthesia, hypoaesthesia facial, and paraesthesia oral), tremor*; **Psychiatric Disorders**—insomnia* (includes middle insomnia, early morning awakening, and initial insomnia), agitation (includes feeling jittery, nervousness, restlessness, tension, and psychomotor hyperactivity); **Reproductive System and Breast Disorders**—erectile dysfunction*, ejaculation disorder; **Respiratory, Thoracic, and Mediastinal Disorders**—cough, oropharyngeal pain*; **Skin and Subcutaneous Tissue Disorders**—hyperhidrosis; **Vascular Disorders**—flushing (includes hot flush).

*Incidence of 120 mg/day is significantly greater than the incidence for 60 mg/day.

Effects on Male and Female Sexual Function—Changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of psychiatric disorders or diabetes, but they may also be a consequence of pharmacologic treatment. Because adverse sexual reactions are presumed to be voluntarily underreported, the Arizona Sexual Experience Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in 4 MDD placebo-controlled trials. In these trials, patients treated with Cymbalta experienced significantly more sexual dysfunction, as measured by the total score on the ASEX, than did patients treated with placebo. Gender analysis showed that this difference occurred only in males. Males treated with Cymbalta experienced more difficulty with ability to reach orgasm (ASEX Item 4) than males treated with placebo. Females did not experience more sexual dysfunction on Cymbalta than on placebo as measured by ASEX total score. Physicians should routinely inquire about possible sexual side effects. (See Table 5 in full PI for specific ASEX results.)

Vital Sign Changes—In placebo-controlled clinical trials across approved indications for change from baseline to endpoint, duloxetine treatment was associated with mean increases of 0.07 mm Hg in systolic blood pressure and 0.62 mm Hg in diastolic blood pressure compared to mean decreases of 1.31 mm Hg systolic and 0.73 mm Hg diastolic in placebo-treated patients. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure [see Warnings and Precautions].

Duloxetine treatment, for up to 26 weeks in placebo-controlled trials across approved indications, typically caused a small increase in heart rate for change from baseline to endpoint compared to placebo of up to 1.40 beats per minute.

Weight Changes—In placebo-controlled clinical trials, MDD and GAD patients treated with Cymbalta for up to 10 weeks experienced a mean weight loss of approximately 0.5 kg compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. In studies of DPNP, FM, OA, and CLBP, patients treated with Cymbalta for up to 26 weeks experienced a mean weight loss of approximately 0.6 kg compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. In one long-term fibromyalgia 60-week uncontrolled study, duloxetine patients had a mean weight increase of 0.7 kg. In one long-term CLBP 54-week study (13-week, placebo-controlled acute phase and 41-week, uncontrolled extension phase), duloxetine patients had a mean weight decrease of 0.6 kg in 13 weeks of acute phase compared to study entry, then a mean weight increase of 1.4 kg in 41 weeks of extension phase compared to end of acute phase.

Laboratory Changes—Cymbalta treatment in placebo-controlled clinical trials across approved indications, was associated with small mean increases from baseline to endpoint in ALT, AST, CPK, and alkaline phosphatase; infrequent, modest, transient, abnormal values were observed for these analytes in Cymbalta-treated patients when compared with placebo-treated patients [see Warnings and Precautions].

Electrocardiogram Changes—Electrocardiograms were obtained from duloxetine-treated patients and placebo-treated patients in clinical trials lasting up to 13 weeks. No clinically significant differences were observed for QTc, QT, PR, and QRS intervals between duloxetine-treated and placebo-treated patients. There were no differences in clinically meaningful QTcF elevations between duloxetine and placebo. In a positive-controlled study in healthy volunteers using duloxetine up to 200 mg twice daily, no prolongation of the corrected QT interval was observed.

Other Adverse Reactions Observed During the Premarketing and Postmarketing Clinical Trial Evaluation of Duloxetine—Following is a list of treatment-emergent adverse reactions reported by patients treated with duloxetine in clinical trials. In clinical trials of all indications, 29,435 patients were treated with duloxetine. Of these, 30.4% (8953) took duloxetine for at least 6 months, and 14.7% (4317) for at least one year. The following listing is