

# Data Sheet

## CYMBALTA<sup>®</sup>

Duloxetine capsules, 30 mg and 60 mg.

### Presentation

CYMBALTA 30 mg capsules have opaque white bodies and opaque blue caps.

CYMBALTA 60 mg capsules have opaque green bodies and opaque blue caps.

CYMBALTA is a delayed-release formulation for oral administration. CYMBALTA 30 mg and 60 mg capsules contains enteric-coated pellets of duloxetine hydrochloride equivalent to 30 mg and 60 mg of duloxetine, respectively. Enteric coating prevents degradation of the medicine within the acidic environment of the stomach.

### Uses

#### *Actions*

Pharmacotherapeutic group: medicines used for the treatment of depression, anxiety and neuropathic pain.

Duloxetine is a combined serotonin (5-HT) and noradrenaline (NA) reuptake inhibitor. It weakly inhibits dopamine reuptake with no significant affinity for histaminergic, dopaminergic, cholinergic and adrenergic receptors. Duloxetine dose-dependently increased extracellular levels of serotonin and noradrenaline in various brain areas of animals.

#### *Pharmacodynamics*

Neurochemical and behavioural studies in laboratory animals showed an enhancement of both serotonin and noradrenaline neurotransmission in the CNS. Duloxetine also normalised pain thresholds in several preclinical models of neuropathic and inflammatory pain and attenuated pain behaviour in a model of persistent pain. The presumed mechanism of action of duloxetine in the treatment of depression is thought to be due to its inhibition of neuronal uptake of serotonin and noradrenaline, and a resultant increase in serotonergic and noradrenergic neurotransmission in the CNS. The pain inhibitory action of duloxetine is believed to be a result of potentiation of descending inhibitory pain pathways within the central nervous system.

#### *Clinical Trials*

Acute treatment of depression:

The efficacy of CYMBALTA was established in six double-blind, placebo-controlled acute Phase 3 studies in 1978 adult outpatients (18 to 83 years) meeting the DSM-IV criteria for major depression at doses of 40 mg to 120 mg daily. In four of these studies, CYMBALTA was significantly superior to placebo as measured by the mean change in the 17-item Hamilton Depression Rating Scale (HAMD-17) total score from baseline to endpoint. The remaining two studies showed numerically superior mean change compared with placebo. In both of these latter studies, the active comparator paroxetine also did not separate significantly from placebo on the primary outcome measure. Response ( $\geq 50\%$  reduction in HAMD-17 total score) and remission (HAMD-17 total score  $\leq 7$ ) were also significantly

higher with CYMBALTA compared with placebo and five out of six and three out of six acute studies, respectively.

While results were positive for improvement in the HAMD-17 at a dose of 40 mg daily in one of two studies, this dose did not demonstrate statistical superiority on any other measure including response or remission.

In addition to the HAMD-17 total score, several other measures were included in the evaluation of efficacy of CYMBALTA. HAMD-17 Depressed Mood Item (Item 1), the Anxiety Subfactor of the HAMD-17, the Patient Global Impressions (PGI) Improvement Score, bodily pain as measured by Visual Analog Scale (VAS), and the Quality of Life in Depression rating scales were also examined. In the four studies where CYMBALTA demonstrated statistical superiority over placebo as measured by improvement in the HAMD-17 total score, results were also positive for the additional measures at doses of 60 mg to 120 mg per day.

Measurements of pain and other bodily symptoms were incorporated into the studies to assess duloxetine's effects on painful physical symptoms that often accompany Major Depressive Disorder (MDD). A superior effect of CYMBALTA compared with placebo on mean change of HAMD-17 Item 13 (a measure of somatic symptoms including pain) was observed. Improvement of painful physical symptoms associated with MDD (VAS overall pain) was consistent with other results, especially at the duloxetine 60 mg once-daily dose.

In each study and in pooled data, the effectiveness of CYMBALTA was similar regardless of age, gender or racial origin.

#### Prevention of depression relapse

Patients responding to 12 weeks of acute treatment with open-label duloxetine at a dose of 60 mg once daily were randomly assigned to either CYMBALTA 60 mg once daily or placebo for a further 6 months (continuation phase) and time to relapse in each group was compared. The estimated probability of depressive relapse at 6 months for placebo was 38.3 and for CYMBALTA 60 mg once daily was 19.7 ( $p=0.004$ ). During the 6-month continuation therapy phase of this study, 17.4% of CYMBALTA-treated patients met the *a priori*-defined criteria for relapse compared with 28.5% on placebo ( $p=0.042$ ).

Of 88 patients who relapsed during the continuation phase, 87 received double blind rescue therapy. Patients relapsing on placebo were treated with CYMBALTA at a dose of 60 mg once daily, and those relapsing on CYMBALTA 60 mg once daily were treated with CYMBALTA 60 mg twice daily. Of those patients relapsing on placebo and treated with CYMBALTA 60 mg once daily, response (50% reduction in HAMD-17 total score) occurred in 77% and remission (HAMD-17 total score  $\leq 7$ ) occurred in 57% at the end of 12 further weeks of treatment. Of those patients who relapsed on CYMBALTA 60 mg once daily and who were treated with an increased dose of 60 mg twice daily, 62% met response criteria and 38% met remission criteria.

#### Use in elderly patients with depression:

The efficacy and safety of duloxetine 60 mg once daily ( $n=207$ ) and placebo ( $n=104$ ) have been compared in the acute treatment (study duration 8 weeks) of elderly patients with MDD ( $>65$  years of age, mean age 72.9 years). Duloxetine treated patients experienced improvement in depressive symptoms, as assessed by the Geriatric Depression Scale, from week 1, with least-squares mean changes from baseline to endpoint of -1.34 for placebo-treated patients and -4.07 for duloxetine-treated patients ( $p<0.001$ ). On the Hamilton Depression Rating Scale, least squares mean changes from baseline to endpoint for total HAMD score were -3.72 for placebo-treated patients and -6.49 for duloxetine-treated patients ( $p<0.001$ ). Duloxetine-treated patients also experienced a greater improvement in composite cognitive score than the

placebo-treated patients. The least-squares mean change from baseline to endpoint for the composite cognitive score was 0.76 in placebo-treated patients and 1.95 for duloxetine-treated patients ( $p=0.013$ ).

## **Diabetic Peripheral Neuropathic Pain**

The efficacy of Cymbalta for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) was established in 2 randomized, 12-week, double-blind, placebo-controlled, fixed-dose studies in adult patients having diabetic peripheral neuropathy for at least 6 months.

The two studies enrolled a total of 792 Patients whom had Type I or II diabetes mellitus with a diagnosis of painful distal symmetrical sensorimotor polyneuropathy for at least 6 months. The patients had a baseline pain score of  $\geq 4$  on an 11-point scale ranging from 0 (no pain) to 10 (worst possible pain).

The weekly mean of the 24-hour average pain severity was the primary efficacy measure for the assessment of duloxetine's effectiveness in the treatment of DPNP. Evidence of efficacy from the primary efficacy measure is confirmed by comprehensive results from the secondary pain and DPNP symptom measures. The secondary efficacy measures that supported the use of CYMBALTA in the treatment of DPNP were: weekly means of night pain and 24-hour worst pain from the daily diary, Brief Pain Inventory Severity and Interference (BPI Severity and Interference), Clinical Global Impressions of Severity (CGI-Severity), Patient Global Impression of Improvement (PGI-Improvement) scale, and Sensory portion of the Short-form McGill pain questionnaire. In addition, measures of mood were employed in both placebo-controlled studies to demonstrate changes of pain uncontaminated by duloxetine's effect on mood

A total of 792 patients were enrolled in both studies, which compared Cymbalta 60 mg once daily or 60 mg twice daily with placebo, with one study additionally comparing Cymbalta 20 mg with placebo Duloxetine 60 mg QD and duloxetine 60 mg BID were both statistically significantly better than placebo in the primary efficacy endpoint, 24-hour pain severity.

Treatment with Cymbalta 60 mg one or two times a day statistically significantly improved the endpoint mean pain scores from baseline and increased the proportion of patients with at least a 50% reduction in pain score from baseline.

For various degrees of improvement in pain from baseline to study endpoint, Figures 1 and 2 show the fraction of patients achieving that degree of improvement. The figures are cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

## Generalised Anxiety Disorder

The efficacy of Cymbalta has been established in 5 Phase 3 clinical trials. Four of the studies were acute placebo-controlled studies and the fifth was a relapse prevention study. Of the four placebo controlled studies one was a fixed dose study while the other three were flexible dose studies.

Study 1 (fixed dose) was a randomised double blind trial designed to assess whether duloxetine 120mg once daily (QD) was superior to placebo in the treatment of GAD as measured by the mean change in Hamilton Anxiety Depression Rating Scale (HAMA) during the 9-week, double-blind, acute therapy phase. A key secondary objective was to assess whether duloxetine 60mg QD was superior to placebo in the treatment of GAD during the 9-week, double blind acute therapy phase

Studies 2, 3 and 4 were Phase 3 (flexible dose) randomised double-blind placebo-controlled studies that used the same primary objective: to assess whether duloxetine flexibly dosed from 60 mg to 120 mg QD was superior to placebo in the treatment of GAD as measured by mean change in HAMA total score over 10 weeks. Venlafaxine 25 mg to 225 mg QD was used as an active comparator in studies 3 and 4 and data from these trials was combined (designed *a priori*) to have sufficient power for non-inferiority comparison of duloxetine with venlafaxine. For all 3 studies doses were increased at specified visits if the CGI-Improvement score remained at 3 or below or minimally improved.

In all 4 acute placebo controlled studies the mean decrease in HAMA total score was significantly greater for duloxetine-treated patients compared with placebo treated patients

### **Pharmacokinetics**

Duloxetine is well absorbed after oral administration with a C<sub>max</sub> occurring 6 hours post dose. Food delays the time to reach the peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11%). Duloxetine is highly protein bound (>90%), primarily to albumin and alpha 1 acid glycoprotein, but protein binding is not affected by renal or hepatic impairment. Duloxetine is extensively metabolised and the metabolites are excreted principally in urine. Both cytochromes P450-CYP2D6 and

P450-CYP1A2 catalyse the formation of the two major metabolites glucuronide conjugate of 4-hydroxy duloxetine and sulphate conjugate of 5-hydroxy, 6-methoxy duloxetine. Based upon in vitro studies, the circulating metabolites of duloxetine are considered pharmacologically inactive. The elimination half-life of duloxetine ranges from 8.1 to 17.4 hours (mean of 12.1 hours). Apparent plasma clearance of duloxetine ranges from 33 to 261 L/hr (mean of 101 L/hr).

### Gender

Although pharmacokinetic differences have been identified between males and females (apparent plasma clearance lower in females), the magnitude of change is not sufficient to justify an adjustment to the dose based upon gender.

## Age

Pharmacokinetic differences have been identified between younger and elderly females (greater than or equal to 65 years) (AUC is higher and half-life is longer in the elderly), although the magnitude of these changes is not sufficient to justify adjustments to the dose.

## Renal Impairment

End stage renal disease (ESRD) patients receiving dialysis had a 2-fold higher duloxetine C<sub>max</sub> and AUC values compared to healthy subjects. Therefore, a lower dose should be considered for patients with clinically significant renal impairment (see Dosage and Administration section).

## Hepatic Impairment

Patients with cirrhosis of the liver had a similar C<sub>max</sub>, but the half-life of duloxetine was 34 hours longer, while clearance was approximately 15% of that for healthy subjects. CYMBALTA is contraindicated in patients with hepatic impairment (see Contraindications).

## Indications

CYMBALTA is indicated for the treatment of major depressive disorder.

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.

CYMBALTA is indicated for the treatment of diabetic peripheral neuropathic pain (DPNP).  
CYMBALTA is indicated for the treatment of generalised anxiety disorder (GAD).

## Dosage and Administration

### Major Depressive Disorder

CYMBALTA should be initiated at a dose of 60 mg once daily without regard to meals. There is no adequate evidence suggesting that patients not responding to 60 mg once daily will benefit from having their dose increased.

### Diabetic Peripheral Neuropathic Pain

Duloxetine should be administered at a dose of 60mg once daily without regard to meals. Some patients may benefit from dosages above the recommended 60mg once daily up to a maximum dose of 120mg per day. Doses above 120 mg have not been systematically evaluated

### Generalised Anxiety Disorder

The recommended starting dose of CYMBALTA in patients with generalized anxiety disorder is 30 mg once daily with or without food. The daily dose should be increased in 30 mg increments until the minimum effective dose is achieved. The maximum dose is 120 mg per day, given as 120 mg once daily. Doses above 120 mg have not been systematically evaluated.

## Initial Tolerability

For patients in whom initial tolerability may be a concern, such as treatment-naïve patients or those with a history of adverse events with other medications, use of a lower starting dose such as 30 mg once daily for one week before increasing the dose to 60 mg once daily should be considered. A dose of 30 mg once daily should be used in patients with end stage renal disease (see below). In addition, clinical studies have shown that taking CYMBALTA with food may improve initial tolerability.

### ***Elderly Patients***

No dosage adjustment is recommended for elderly patients solely on the basis of age.

### ***Children***

The safety and efficacy of duloxetine in patients under the age of 18 years have not been studied.

### ***Patients with Renal Impairment***

Initial dosage should be 30 mg once daily in patients with end stage renal disease (ESRD) (creatinine clearance <30 mL/min). (See Warnings and Precautions section).

### ***Patients with Hepatic Impairment***

CYMBALTA is contraindicated in patients with liver disease resulting in hepatic impairment (see Contraindications).

### ***Discontinuation of treatment***

When discontinuing CYMBALTA after more than one week of therapy it is generally recommended that the dose be tapered to minimise the risk of discontinuation symptoms. As a general recommendation, the dose of CYMBALTA should be reduced by half or administered on alternate days during a period of not less than two weeks. The precise regimen followed should take into account the individual circumstances of the patient, such as duration of treatment, dose at discontinuation, etc.

## **Contraindications**

CYMBALTA is contraindicated in patients known to be hypersensitive to duloxetine or to any of the excipients.

CYMBALTA should not be used in combination with monoamine oxidase inhibitors (MAOIs), or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping CYMBALTA before starting an MAOI.

CYMBALTA is contraindicated in patients with liver disease resulting in hepatic impairment (see Pharmacokinetics)

CYMBALTA should not be used in combination with potent CYP1A2 inhibitors (see Drug Interactions).

## Warnings and Precautions

### ***Clinical Worsening and Suicide Risk***

The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany treatment. Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms. Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. Patients with co-morbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Pooled analyses of 24 short-term (4 to 16 weeks), placebo-controlled trials of nine antidepressant medicines (SSRIs and others) in 4400 children and adolescents with major depressive disorder (16 trials), obsessive compulsive disorder (4 trials) or other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4% compared with 2% of patients given placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medications in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (bupropion, mirtazapine, nefazodone, venlafaxine).

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania and mania have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Families and caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or nonpsychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

Prescriptions for CYMBALTA should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

### ***Hepatotoxicity***

CYMBALTA should ordinarily not be prescribed to patients with evidence of chronic liver disease as it is possible that duloxetine may aggravate pre existing liver disease (see Contraindications).

CYMBALTA increases the risk of elevation of serum transaminase levels. Liver transaminase elevations resulted in the discontinuation of 0.3% (82/27,229) of CYMBALTA-treated patients. In these patients, the median time to detection of the transaminase elevation was about two months. In placebo controlled trials in any indication, elevations of alanine transaminase (ALT) to >3 times the upper limit of normal occurred in 1.1% (85/7632) of CYMBALTA-treated patients and in 0.2% (13/5578) of placebo treated patients. In the full cohort of placebo-controlled trials in any indication, elevation of ALT >3 times the upper limit of normal occurred in 1% (39/3732) of CYMBALTA-treated patients 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. Isolated cases of liver failure, including fatal cases, have been reported. A majority of these cases have been reported in patients with past or current risk factors for liver injury, including alcohol abuse, hepatitis or exposure to drugs with known adverse effects on the liver.

The combination of transaminase elevations and elevated bilirubin, without evidence of obstruction, is generally recognised 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.

Postmarketing reports indicate that elevated transaminases, bilirubin and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis.

### **Alcohol**

Use of CYMBALTA with substantial alcohol consumption may be associated with severe liver injury. Isolated cases of liver failure, including fatal cases, have been reported (see Warnings and Precautions – Hepatotoxicity). CYMBALTA should only be used in exceptional circumstances with extreme caution in patients who consume substantial amounts of alcohol.

### **Mania, seizures**

In placebo-controlled trials in patients with major depressive disorder, activation of hypomania or mania occurred in 0.1% of duloxetine treated patients and 0.1% of placebo treated patients. Activation of mania/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 similar CNS active medicines, duloxetine should be used with caution in patients with a history of mania or a diagnosis of bipolar disorder, and/or seizures.

### **Mydriasis**

Mydriasis has been reported in association with duloxetine, therefore, caution should be used when prescribing duloxetine in patients with raised intraocular pressure, or those at risk of acute narrow-angle glaucoma.

### **Hyponatraemia**

Hyponatraemia has been reported very rarely, predominantly in the elderly, when administering CYMBALTA. Caution is required in patients at increased risk for hyponatraemia; such as elderly, cirrhotic, or dehydrated patients or patients treated with diuretics. Hyponatraemia may be due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

### **Use in Patients with Concomitant Illness**

Clinical experience with duloxetine in patients with concomitant systemic illnesses is limited. Caution is advisable in using duloxetine in patients with diseases or conditions that produce altered metabolism or haemodynamic responses.

Duloxetine has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. However, evaluation of electrocardiograms (ECGs) of 321 patients who received duloxetine in placebo-controlled clinical trials indicated that duloxetine is not associated with the development of clinically significant ECG abnormalities (see Warnings and Precautions-Electrocardiograms).

Increased plasma concentrations of duloxetine occur in patients with end stage renal disease (ESRD) and in patients with moderate hepatic impairment (see Pharmacokinetics).

### **Use in patients with renal impairment**

Increased plasma concentrations of duloxetine occur in patients with severe renal impairment (creatinine clearance <30 mL/min). A lower starting dose should be used in such patients if clinically relevant (see Dosage and Administration and Pharmacokinetics sections) Population pharmacokinetic analyses suggest that mild renal dysfunction has no significant effect on apparent plasma clearance of duloxetine.

### ***Increase in blood pressure***

Duloxetine is associated with an increase in blood pressure in some patients. In clinical trials, duloxetine treatment was associated with increases in blood pressure, averaging 2 mm Hg systolic and 0.5 mm Hg diastolic compared to placebo (see Adverse Effects). Large, potentially clinically significant, elevations in blood pressure do not appear to be more common with duloxetine than with placebo. In patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended as appropriate. CYMBALTA should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure.

### ***Orthostatic Hypotension and Syncope***

Orthostatic hypotension and syncope have been reported with therapeutic doses of duloxetine. Syncope and hypotension tend to occur within the first week of therapy but can occur at any time during duloxetine treatment, particularly after dose increases. The risk of blood pressure decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as antihypertensives) or are potent CYP1A2 inhibitors and in patients taking doses above 60 mg daily. Consideration should be given to discontinuing CYMBALTA in patients who experience symptomatic orthostatic hypotension and/or syncope during therapy.

### ***Electrocardiograms***

Electrocardiograms were obtained from 321 duloxetine-treated patients with MDD and 169 placebo-treated patients in clinical trials lasting up to 8 weeks. The rate-corrected QT (QTc) interval in duloxetine-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, and QRS intervals between duloxetine-treated and placebo-treated patients.

### ***Discontinuing Treatment***

As with other medicines effective in the treatment of major depressive disorder, when discontinuing CYMBALTA after more than 1 week of therapy, it is generally recommended that the dose be tapered to minimise the risk of discontinuation symptoms (see Dosage and Administration). The most commonly reported symptoms following abrupt discontinuation of duloxetine in clinical trials have included dizziness, nausea, headache, paraesthesia, vomiting, irritability, nightmares, insomnia, diarrhoea, anxiety, hyperhidrosis and vertigo.

### ***Serotonin Syndrome***

In rare cases serotonin syndrome has been reported in patients using SSRIs (e.g. paroxetine, fluoxetine) concomitantly with serotonergic medicinal products. Caution is advisable if CYMBALTA is used concomitantly with serotonergic antidepressants like SSRIs, tricyclics like clomipramine or amitriptyline, St John's Wort (*Hypericum perforatum*), venlafaxine or triptans, tramadol, pethidine and tryptophan.

### ***Drug Dependence***

While duloxetine has not been systematically studied in humans for its potential for abuse, there was no indication of drug-seeking behaviour in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of duloxetine (e.g. development of tolerance, incrementation of dose, drug-seeking behaviour).

### ***Weight Changes***

Weight changes do not appear to be clinically significant outcomes of treatment with duloxetine. In placebo-controlled clinical trials, patients treated with duloxetine for up to 9-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.

### ***Carcinogenicity, Mutagenesis, Impairment of Fertility***

Duloxetine was not genotoxic in a standard battery of tests and produced no teratogenic effects in rats or rabbits. Duloxetine did not cause an increase in the incidence of neoplasms in rats. Female mice receiving duloxetine for 2 years had an increased incidence of hepatocellular adenomas and carcinomas at the high dose only (144 mg/kg/day), but these were considered to be secondary to hepatic enzyme induction with associated centrilobular hypertrophy and vacuolation. The relevance of this mouse data to humans is unknown. Reproductive performance was not affected in male rats receiving duloxetine (45 mg/kg/day). Female rats receiving duloxetine (45 mg/kg/day), had a decrease in maternal food consumption and body weight, oestrous cycle disruption, depressions in live birth indices and progeny survival, and progeny growth retardation. The no-observed-effect level (NOEL) for maternal toxicity, reproductive toxicity, and developmental toxicity in the female fertility study was 10 mg/kg/day.

### ***Pregnancy and Lactation***

The safety of duloxetine for use in human pregnancy has not been established, therefore CYMBALTA should be used in pregnant women only if the expected benefit justifies the potential risk to the foetus. Women should be advised to notify their physician if they become pregnant, or intend to become pregnant during therapy. There was no evidence of teratogenicity in animal studies.

Duloxetine is excreted into the milk of lactating women. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose. Administration of CYMBALTA to nursing mothers is not recommended.

### ***Effects on Ability to Drive and Use Machinery***

Although in controlled studies duloxetine has not been shown to impair psychomotor performance, cognitive function, or memory, it may be associated with sedation. Therefore, patients should be cautioned about their ability to drive a car or operate hazardous machinery.

## **Adverse Effects**

The following information on adverse effects is based on adverse event reporting and laboratory investigations from clinical trials of duloxetine in 9445 patients with depression or other indications. Very common events are defined as those occurring in  $\geq 10\%$  of patients, common events are defined as those occurring in  $\geq 1\%$  and  $< 10\%$  of patients, uncommon events are defined as those occurring in  $\geq 0.1\%$  and  $< 1\%$  of patients and rare events are defined as those occurring in  $< 0.1\%$  of patients.

### Cardiac Disorders:

*Common:* Palpitations *Uncommon:* tachycardia.

### Ear and Labyrinth Disorders:

*Uncommon:* vertigo, ear pain, tinnitus

### Endocrine Disorders

*Rare:* hypothyroidism.

Eye Disorders:

*Common:* Vision blurred *Uncommon:* mydriasis, visual disturbance.

Gastrointestinal Disorders:

*Very Common:* Nausea, dry mouth, diarrhoea, constipation, *Common:* abdominal pain, vomiting, dyspepsia, loose stools. *Uncommon:* eructation, gastroenteritis, stomatitis, halitosis, gastritis.

General Disorders and Administration Site Conditions:

*Very common:* Fatigue. *Common:* Asthenia, pyrexia. *Uncommon:* feeling abnormal, feeling cold, feeling hot, malaise, thirst; *Rare:* gait disturbance.

Infections and Infestations

*Common:* Nasopharyngitis. *Uncommon:* laryngitis

Investigations:

*Common:* Weight increased, weight decreased. *Uncommon:* blood pressure increased (including blood pressure systolic increased and blood pressure diastolic increased), hepatic lab related findings (including alanine aminotransferase increased, hepatic enzyme increased, aspartate aminotransferase increased, liver function test abnormal, gamma-glutamyltransferase increased, blood alkaline phosphatase increased, blood bilirubin increased), weight increased, blood cholesterol increased.

Metabolism and Nutrition Disorders:

*Common:* Decreased appetite, anorexia. *Uncommon:* dehydration

Musculoskeletal and Connective Tissue Disorders:

*Common:* Muscle cramp, myalgia, musculoskeletal pain, muscle spasms. *Uncommon:* muscle tightness, muscle twitching.

Nervous System Disorders:

*Very Common:* Dizziness, somnolence, headache. *Common:* Tremor, parasthesia, dysgeusia. *Uncommon:* disturbance in attention, dyskinesia, poor quality sleep; *Rare:* myoclonus.

Psychiatric Disorders:

*Common:* Insomnia, agitation (including feeling jittery, nervousness, restlessness, tension, psychomotor agitation), anxiety, libido decreased (including loss of libido), orgasm abnormal (including anorgasmia), abnormal dreams (including nightmares). *Uncommon:* bruxism, disorientation (including confusional state), apathy.

Renal and Urinary Disorders:

*Uncommon:* nocturia, urinary hesitation, urinary retention, dysuria, polyuria; *Rare:* urine odour abnormal, urine flow decreased.

Duloxetine is in a class of medicines known to affect urethral resistance. In placebo-controlled clinical trials in patients with major depressive disorder, urinary hesitation was reported rarely (<1%) in male patients only. If symptoms of urinary hesitation develop during treatment with duloxetine, consideration should be given to the possibility that they might be medicine-related.

#### Reproductive System and Breast Disorders:

*Common:* Erectile dysfunction, ejaculation delayed, ejaculation disorder. *Uncommon:* ejaculation delayed, menopausal symptoms, erectile dysfunction, sexual dysfunction.

#### Respiratory, Thoracic and Mediastinal Disorders:

*Common:* yawning, cough, pharyngolaryngeal pain. *Uncommon:* throat tightness

#### Skin and Subcutaneous Tissue Disorders:

*Common:* Hyperhidrosis, rash, pruritis. *Uncommon:* night sweats, photosensitivity reaction, cold sweat, dermatitis contact.

#### Vascular Disorders:

*Common:* Hot flush. *Uncommon:* peripheral coldness, orthostatic hypotension

#### Discontinuation symptoms

Dizziness, nausea and headache (greater than or equal to 5%) were also reported as common adverse events upon duloxetine discontinuation. Discontinuation symptoms have been reported when stopping duloxetine. Symptoms may include dizziness, nausea, headache, paraesthesia, vomiting, irritability, insomnia, diarrhoea, anxiety, hyperhidrosis, vertigo and nightmares (see Warnings and Precautions).

#### ECG Abnormalities

Electrocardiograms were obtained from 321 duloxetine-treated patients in placebo-controlled clinical trials. The data indicate that duloxetine is not associated with the development of clinically significant ECG abnormalities (see Warnings and Precautions).

#### Blood Pressure

In placebo-controlled clinical trials of up to 9 weeks duration, duloxetine treatment was associated with a small increase in heart rate of about 2 beats per minute and increases in blood pressure averaging 2 mm Hg systolic and 0.5 mm Hg diastolic compared with placebo.

#### Blood Glucose

In three clinical trials of duloxetine for the treatment of diabetic neuropathic pain, the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 176 mg/dL, and the mean baseline haemoglobin HbA1c was 7.81%. In the 12 week acute treatment phase of these studies, small increases in fasting blood glucose were observed in duloxetine-treated patients. HbA1c was stable in both duloxetine-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52

weeks, there was an increase in HbA1c in both the duloxetine and the routine care groups, but the mean increase was 0.3% greater in the duloxetine-treated group. There was also a small increase in fasting blood glucose and in total cholesterol in duloxetine-treated patients while those laboratory tests showed a slight decrease in the routine care group.

### ***Spontaneous Data***

The following list of adverse drug reactions is based on postmarketing spontaneous reports, and corresponding reporting rates have been provided. Rare events are defined as those occurring in less than 1/1000 patients; very rare events are those occurring in less than 1/10,000 patients.

#### Endocrine disorders

*Very rare:* SIADH

#### Cardiac disorders

*Very rare:* supraventricular tachycardia

#### Ear and Labyrinth disorders

*Very rare:* Tinnitus upon treatment discontinuation

#### Eye disorders

*Very rare:* glaucoma

#### Hepatobiliary disorders

*Very rare:* alanine aminotransferase increased, alkaline phosphatase increased, aspartate aminotransferase increased, bilirubin increased, hepatitis, jaundice

Isolated cases of liver failure, including fatal cases, have been reported. A majority of these cases have been reported in patients with past or current risk factors for liver injury, including alcohol abuse, hepatitis or exposure to drugs with known adverse effects on the liver. (see Warnings and Precautions)

#### Immune system disorders

*Very rare:* anaphylactic reaction, hypersensitivity

#### Metabolism and nutrition disorders

*Very rare:* hyponatraemia, hypoglycaemia (reported especially in diabetic patients)

#### Musculoskeletal and connective tissue disorders

*Very rare:* trismus, muscle spasm

#### Nervous system disorders

*Very rare:* extrapyramidal disorder, serotonin syndrome, seizures

#### Psychiatric disorders

*Rare*: hallucinations; *Very rare*: mania, aggression and anger (particularly early in treatment or after treatment discontinuations)

#### Renal and urinary disorders

*Rare*: urinary retention

#### Skin and subcutaneous tissue disorders

*Rare*: rash; *Very rare*: angioneurotic oedema, contusion, ecchymosis, Stevens-Johnson Syndrome, urticaria

#### Vascular disorders

*Very rare*: orthostatic hypotension (especially at the initiation of treatment), syncope (especially at initiation of treatment), hypertensive crisis

## Interactions

Duloxetine is a SNRI with its primary effect on the CNS. Caution should be used when it is administered in combination with other centrally acting drugs and substances, especially those with a similar mechanism of action, including alcohol. Concurrent use with other drugs with serotonergic activity (eg SNRIs, SSRIs, triptans or tramadol) may result in serotonin syndrome (see Warnings and Precautions).

Although duloxetine does not increase the impairment of mental and motor skills caused by alcohol, use of CYMBALTA with substantial alcohol consumption may be associated with severe liver injury. Isolated cases of liver failure, including fatal cases, have been reported (see Warnings and Precautions – Hepatotoxicity). CYMBALTA should only be used in exceptional circumstances with extreme caution in patients who consume substantial amounts of alcohol.

**Medicines metabolised by CYP1A2:** in a clinical study, the pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by co-administration with duloxetine (60 mg twice daily). These results suggest that duloxetine is unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates.

**Inhibitors of CYP1A2:** because CYP1A2 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP1A2 will likely result in higher concentrations of duloxetine. Fluvoxamine (100 mg once daily), a potent inhibitor of CYP1A2, decreased the apparent plasma concentration of duloxetine by about 77%. CYMBALTA should not be used in combination with potent inhibitors of CYP1A2 (e.g., fluvoxamine) (see Contraindications).

**Medicines metabolised by CYP2D6:** duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered at a dose of 60 mg twice daily with a single dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. The co-administration of duloxetine (40 mg twice daily) increases steady state AUC of tolterodine (2 mg twice daily) by 71% but does not affect the pharmacokinetics of its 5-hydroxyl metabolite. Therefore, caution should be used if duloxetine is co-administered with medications that are predominantly metabolised by CYP2D6 and which have a narrow therapeutic index (e.g. tricyclic antidepressants such as nortriptyline and imipramine, phenothiazines, flecainide, propafenone). Because of the risk of serious ventricular arrhythmias and sudden death

potentially associated with elevated plasma concentrations of thioridazine, CYMBALTA and thioridazine should not be coadministered..

**Inhibitors of CYP2D6:** because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 may result in higher concentrations of duloxetine. Paroxetine (20 mg once daily) decreased the apparent plasma clearance of duloxetine by about 37%. Caution is advised if administering duloxetine with inhibitors of CYP2D6 (e.g., SSRIs).

**CNS medicines:** caution is advised when duloxetine is taken in combination with other centrally acting medicines or substances, especially those with a similar mechanism of action, and including alcohol. Concomitant use of other agents with serotonergic activity (e.g., SNRIs, SSRIs, triptans or tramadol) may result in serotonin syndrome.

**Monoamine Oxidase Inhibitors (MAOI)** - Because duloxetine is an inhibitor of both serotonin and noradrenaline reuptake, it is recommended that duloxetine not be used in combination with an MAOI (see Contraindications)

**Antacids and H2 antagonists:** co-administration of duloxetine with aluminium- and magnesium-containing antacids or duloxetine with famotidine had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose.

**St John's Wort** - In common with other antidepressants, concomitant administration of duloxetine and the herbal remedy St John's Wort (*Hypericum perforatum*) is not recommended.

**Warfarin and INR** – Increases in INR have been reported when duloxetine was co-administered with warfarin.

**Lorazepam:** under steady-state conditions, duloxetine had no effect on lorazepam kinetics and lorazepam had no effect on duloxetine kinetics. The combination of duloxetine and lorazepam resulted in increased sedation compared with lorazepam alone.

**Oral contraceptives and other steroidal agents:** results of in vitro studies demonstrate that duloxetine does not inhibit or induce the catalytic activity of CYP3A. No increase or decrease in the metabolism of CYP3A substrates (e.g. oral contraceptives and other steroidal agents) is anticipated.

## Overdosage

There is limited clinical experience with duloxetine overdose in humans. In pre-marketing clinical trials, cases of acute ingestion up to 1400 mg, alone or in combination with other drugs, were reported with none being fatal. Postmarketing experience includes reports of overdoses, alone or in combination with other drugs, with duloxetine doses of almost 2000 mg. Fatalities have been very rarely reported, primarily with mixed overdoses, but also with duloxetine alone at a dose of approximately 1000 mg. Signs and symptoms of overdose (most with mixed drugs) included serotonin syndrome, somnolence, vomiting, and seizures.

In animal studies, the major signs of overdose toxicity are related to the central nervous and gastrointestinal systems. These include central nervous system effects such as tremors, clonic convulsions, ataxia, emesis, and decreased appetite.

No specific antidote is known, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. An airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate

symptomatic and supportive measures. Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal may be useful in limiting absorption. Duloxetine has a large volume of distribution and forced diuresis, haemoperfusion, and exchange perfusion are unlikely to be beneficial.

## **Pharmaceutical Precautions**

### **Storage**

Store below 25°C in the original package.

### **Shelf Life**

2 years.

### **Instructions for Use and Handling**

No special requirements.

### **Major Incompatibilities**

Not applicable.

### **Medicine Classification**

Prescription Medicine.

### **Package Quantities**

CYMBALTA capsules are blister packaged and are available in cartons containing 7 or 28 capsules.

### **Further Information**

#### Excipients

Gelatin, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate succinate, sodium lauryl sulphate, sucrose, sugar spheres, talc, titanium dioxide, and triethyl citrate, indigo carmine. The 60 mg capsules also contain iron oxide yellow.

### **Name and Address**

Eli Lilly and Company (NZ) Limited  
Level 3, Axon House, 414-422 Khyber Pass Road  
PO Box 109197  
Newmarket, Auckland  
NEW ZEALAND.  
Telephone (09) 523 9300

### **Date of Preparation**

12<sup>th</sup> May 2011