Lilly

1. NAME OF THE MEDICINAL PRODUCT

Cymbalta capsules 30mg
Cymbalta capsules 60mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cymbalta 30mg
Each capsule contains 30 mg of duloxetine (as hydrochloride).

Excipient(s) with known effect
Each capsule may contain up to 56 mg sucrose.

Cymbalta 60mg
Each capsule contains 60 mg of duloxetine (as hydrochloride).

Excipient(s) with known effect
Each capsule may contain up to 111 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gastro-resistant capsule.
Cymbalta 30mg
Opaque white body, imprinted with '30 mg' and an opaque blue cap, imprinted with '9543'.

Cymbalta 60mg
Opaque green body, imprinted with '60 mg' and an opaque blue cap, imprinted with '9542'.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of major depressive disorder.
Treatment of generalised anxiety disorder.
Treatment of diabetic peripheral neuropathic pain.Management of pain associated with fibromyalgia.

Cymbalta is not indicated for use in children and adolescents below 18 years of age.

4.2 Posology and method of administration

For oral use, with or without food. Cymbalta should be swallowed whole and should not be chewed or crushed, nor should the capsule be opened and its contents sprinkled on food or mixed with liquids. All of these might affect the enteric coating.

Major depressive disorder
The starting and recommended maintenance dose is 60 mg once daily. Dosages above 60 mg once daily, up to a maximum dose of 120 mg/day administered in evenly divided doses, have been evaluated from a safety perspective in clinical trials. However, there is no clinical evidence suggesting that patients not responding to the initial recommended dose may benefit from dose up-titrations.

Therapeutic response is usually seen after 2-4 weeks of treatment.

After consolidation of the antidepressive response, it is recommended to continue treatment for several months, in order to avoid relapse. In patients responding to duloxetine, and with a history of repeated episodes of major depression, further long-term treatment at a dose of 60 to 120 mg/day could be considered.

Generalised anxiety disorder
For most patients, the recommended starting dose for Cymbalta is 60 mg administered once daily. For some patients, it may be desirable to start at 30 mg once daily for 1 week, to allow patients to adjust to the medication before increasing to 60 mg once daily. While a 120 mg once daily dose was shown to be effective, there is no evidence that doses greater than 60 mg once daily confer additional benefit. Nevertheless, if a decision is made to increase the dose beyond 60 mg once daily, dose increases should be in increments of 30 mg once daily. The safety of doses above 120 mg once daily has not been adequately evaluated.

Diabetic peripheral neuropathic pain
The starting and recommended maintenance dose is 60 mg daily. While a dose up to 120mg/day was shown to be safe and effective, there is no evidence that doses higher than 60mg confer additional significant benefit, and the higher dose is clearly less well tolerated. For patients for whom tolerability is a concern, a lower starting dose may be considered. Since diabetes is frequently complicated by renal disease, a lower starting dose and gradual increase in dose should be considered for patients with renal impairment. As the progression of diabetic peripheral neuropathy is highly variable and management of pain is empirical, the effectiveness of Cymbalta must be assessed individually. Efficacy beyond 12 weeks has not been systemically studied in placebo-controlled trials, but a 1-year open-label safety study was conducted.

Response to treatment should be evaluated after 2 months. In patients with inadequate initial response, additional response after this time is unlikely.

The therapeutic benefit should be reassessed regularly (at least every three months) (see section 5.1).

Fibromyalgia
The recommended dose for Cymbalta is 60 mg once daily. Treatment may begin at 30 mg once daily for 1 week, to allow patients to adjust to the medication before increasing to 60 mg once daily. There is limited evidence that doses greater than 60 mg/day confer additional benefit, even in patients who do not respond to a 60 mg dose, and higher doses are associated with a higher rate of adverse reactions. The safety of doses above 120 mg once daily has not been evaluated in fibromyalgia. The efficacy of Cymbalta in the management of fibromyalgia has been demonstrated in placebo-controlled studies up to 3 months. The efficacy of Cymbalta was not demonstrated in longer studies; however, continued treatment should be based on individual patient response.

Elderly
No dosage adjustment is recommended for elderly patients solely on the basis of age. However, as with any medicine, caution should be exercised when treating the elderly, especially with Cymbalta 120 mg per day for major depressive disorder or generalised anxiety disorder, for which data are limited (see sections 4.4, 5.1 and 5.2).

Hepatic impairment
Cymbalta must not be used in patients with liver disease resulting in hepatic impairment (see sections 4.3 and 5.2).

Renal impairment
No dosage adjustment is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 ml/min). See section 4.3 for patients with severe renal impairment.

Paediatric population
Cymbalta should not be used in children and adolescents under the age of 18 years for the treatment of major depressive disorder because of safety and efficacy concerns (see sections 4.4).

The safety and efficacy of Cymbalta for the treatment of diabetic peripheral neuropathic pain or generalised anxiety disorder have not been established.

Therefore, administration of Cymbalta to children and adolescents is not recommended.

Discontinuation of treatment
Abrupt discontinuation should be avoided. When stopping treatment with Cymbalta the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 and 4.8). 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.

4.3 Contraindications

Hypersensitivity to duloxetine or to any of the excipients.

Concomitant use of Cymbalta with non-selective, irreversible monoamine oxidase inhibitors (MAOIs) is contraindicated (see section 4.5).

Patients with pre-existing liver diseases, patients with substantial alcohol use or evidence of chronic liver disease (see sections 4.4 and section 5.2).

Cymbalta should not be used in combination with fluvoxamine, ciprofloxacin or enoxacin (i.e. potent CYP1A2 inhibitors) since the combination results in elevated plasma concentrations of Cymbalta (see section 4.5).

Severe renal impairment (creatinine clearance <30 ml/min) (see section 4.4).

The initiation of treatment with Cymbalta is contraindicated in patients with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Mania and seizures
Cymbalta 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 Cymbalta, therefore, caution should be used when prescribing Cymbalta to patients with increased intraocular pressure, or those at risk of acute narrow-angle glaucoma.

Blood pressure and heart rate
Cymbalta has been associated with an increase in blood pressure and clinically significant hypertension in some patients. This may be due to the noradrenergic effect of Cymbalta. Cases of hypertensive crisis have been reported with Cymbalta, especially in patients with pre-existing hypertension. Therefore, in patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended, especially during the first month of treatment. Cymbalta should be used with caution in patients whose conditions could be compromised by an increased heart rate or blood pressure. Caution should also be exercised when Cymbalta is used with medicinal products that may impair its metabolism (see section 4.5). For patients who experience a sustained increase in blood pressure while receiving Cymbalta, either dose reduction or gradual discontinuation should be considered (see section 4.8). In patients with uncontrolled hypertension Cymbalta should not be initiated (see section 4.3).

Renal impairment
Increased plasma concentrations of Cymbalta occur in patients with severe renal impairment on haemodialysis (creatinine clearance <30 ml/min). For patients with severe renal impairment, see section 4.3. See section 4.2 for information on patients with mild or moderate renal dysfunction.

Serotonin syndrome
As with other serotonergic agents, serotonin syndrome, a potentially life-threatening condition, may occur with Cymbalta treatment, particularly with concomitant use of other serotonergic agents [including selective serotonin reuptake inhibitors (SSRIs), serotonin/noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) or triptans], with agents that impair metabolism of serotonin such as MAOIs, or with antipsychotics or other dopamine antagonists that may affect the serotonergic neurotransmitter systems (see sections 4.3 and 4.5).

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, diarrhoea).

If concomitant treatment with Cymbalta and other serotonergic agents that may affect the serotonergic and/or dopaminergic neurotransmitter systems is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

St John's wort
Adverse reactions may be more common during concomitant use of Cymbalta and herbal preparations containing St John's wort (Hypericum perforatum).

Suicide
Major Depressive Disorder and Generalised Anxiety Disorder: Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which Cymbalta is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal thoughts prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicidal behaviour, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant medicinal products in psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Cases of suicidal thoughts and suicidal behaviours have been reported during Cymbalta therapy or early after treatment discontinuation (see section 4.8).

Close supervision of patients and in particular those at high risk should accompany medicinal product therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Diabetic Peripheral Neuropathic Pain: As with other medicinal products with similar pharmacological action (antidepressants), isolated cases of suicidal ideation and suicidal behaviours have been reported during Cymbalta therapy or early after treatment discontinuation. Concerning risk factors for suicidality in depression, see above. Physicians should encourage patients to report any distressing thoughts or feelings at any time.

Use in children and adolescents under 18 years of age
Cymbalta should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempts and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger), were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking (see section 4.8).

Haemorrhage
There have been reports of bleeding abnormalities, such as ecchymoses, purpura and gastrointestinal haemorrhage with SSRIs and SRNIs, including Cymbalta. Cymbalta may increase the risk of postpartum haemorrhage (see section 4.6). Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function (e.g. NSAIDs or aspirin), and in patients with known bleeding tendencies.

Hyponatraemia
Hyponatraemia has been reported when administering Cymbalta, including cases with serum sodium lower than 110 mmol/l. Hyponatraemia may be due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH). The majority of cases of hyponatraemia were reported in the elderly, especially when coupled with a recent history of, or condition pre-disposing to, altered fluid balance. Caution is required in patients at increased risk for hyponatraemia, such as elderly, cirrhotic, or dehydrated patients or patients treated with diuretics. Discontinuation of Cymbalta should be considered in patients with symptomatic hyponatraemia and appropriate medical intervention should be instituted.

Discontinuation of treatment
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In clinical trials adverse events seen on abrupt treatment discontinuation occurred in approximately 45% of patients treated with Cymbalta and 23% of patients taking placebo. The risk of withdrawal symptoms seen with SSRIs and SNRIs may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. The most commonly reported reactions are listed in section 4.8. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that Cymbalta should be gradually tapered when discontinuing treatment over a period of no less than 2 weeks, according to the patient's needs (see section 4.2).

Elderly
Data on the use of Cymbalta 120 mg in elderly patients with major depressive disorder and generalised anxiety disorder are limited. Therefore, caution should be exercised when treating the elderly with the maximum dosage (see sections 4.2, 5.1 and 5.2).

Fibromyalgia: Of the 1,761 patients in fibromyalgia premarketing studies, 7.9% (140) were 65 years of age or over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. However, as with all drugs, greater sensitivity of some older individuals cannot be ruled out.

Akathisia/psychomotor restlessness
The use of Cymbalta has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Medicinal products containing duloxetine
Duloxetine is used under different trademarks in several indications (treatment of diabetic peripheralneuropathic pain, major depressive disorder, generalised anxiety disorder and stress urinary incontinence). The use of more than one of these products concomitantly should be avoided.

Hepatitis/increased liver enzymes
Cases of liver injury, including severe elevations of liver enzymes (>10 times upper limit of normal), hepatitis and jaundice have been reported with Cymbalta (see section 4.8). Most of them occurred during the first months of treatment. The pattern of liver damage was predominantly hepatocellular. Cymbalta should be used with caution in patients treated with other medicinal products associated with hepatic injury.

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 ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Patients prescribed Cymbalta should be warned to report any symptoms of liver dysfunction e.g., pruritus, dark urine, jaundice, right upper quadrant tenderness or unexplained flu-like symptoms. Cymbalta should be discontinued in patients with jaundice or laboratory evidence of liver injury. Excessive alcohol consumption should be avoided during treatment with Cymbalta.

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

Sexual dysfunction
Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (see section 4.8). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRIs.

Sucrose
Cymbalta hard gastro-resistant capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine oxidase inhibitors (MAOIs): Due to the risk of serotonin syndrome, Cymbalta should not be used in combination with non-selective irreversible MAOIs), or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of Cymbalta, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI (see section 4.3).

The concomitant use of Cymbalta with selective, reversible MAOIs, like moclobemide, is not recommended (see section 4.4). The antibiotic linezolid is a reversible non-selective MAOI and should not be given to patients treated with Cymbalta (see section 4.4).

Inhibitors of CYP1A2: Because CYP1A2 is involved in Cymbalta metabolism, concomitant use of Cymbalta with potent inhibitors of CYP1A2 is likely to result in higher concentrations of Cymbalta. Fluvoxamine (100 mg once daily), a potent inhibitor of CYP1A2, decreased the apparent plasma clearance of Cymbalta by about 77% and increased AUC_{o-t} 6-fold. Therefore Cymbalta should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine (see section 4.3).

CNS medicinal products: The risk of using Cymbalta in combination with other CNS-active medicinal products has not been systematically evaluated, except in the cases described in this section. Consequently, caution is advised when Cymbalta is taken in combination with other centrally acting medicinal products or substances, including alcohol and sedative medicinal products (e.g. benzodiazepines, morphinomimetics, antipsychotics, phenobarbital, sedative antihistamines).

Serotonergic agents: In rare cases, serotonin syndrome has been reported in patients using SSRIs/SNRIs concomitantly with serotonergic agents. Caution is advisable if Cymbalta is used concomitantly with serotonergic agents like SSRIs, SNRIs, TCAs like clomipramine or amitriptyline, MAOIs like moclobemide or linezolid, St John's wort (Hypericum perforatum) or triptans, tramadol, pethidine and tryptophan (see section 4.4).

Effect of Cymbalta on other medicinal products
Medicinal products metabolised by CYP1A2: The pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by co-administration with Cymbalta (60 mg twice daily). The study was performed in males and it cannot be excluded that females having a lower CYP1A2 activity and higher plasma concentrations of Cymbalta may experience an interaction with a CYP1A2 substrate.

Medicinal products metabolised by CYP2D6: Cymbalta is a moderate inhibitor of CYP2D6. When Cymbalta 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 Cymbalta (40 mg twice daily) increases steady state AUC of tolterodine (2 mg twice daily) by 71 %, but does not affect the pharmacokinetics of its active 5-hydroxyl metabolite and no dosage adjustment is recommended. Caution is advised if Cymbalta is co-administered with medicinal products that are predominantly metabolised by CYP2D6 (risperidone, TCAs such as nortriptyline, amitriptyline, and imipramine) particularly if they have a narrow therapeutic index (such as flecainide, propafenone and metoprolol).

Drugs highly bound to plasma proteins: Addition of Cymbalta with another drug that is highly bound to plasma proteins may increase free concentrations of the other drug, potentially resulting in adverse events.

Oral contraceptives and other steroidal agents: Results of *in vitro* studies demonstrate that Cymbalta does not induce the catalytic activity of CYP3A. Specific *in vivo* drug interaction studies have not been performed.

Anticoagulants and antiplatelet agents: Caution should be exercised when Cymbalta is combined with oral anticoagulants or antiplatelet agents due to a potential increased risk of bleeding attributable to a pharmacodynamic interaction. Furthermore, increases in INR values have been reported when Cymbalta was co-administered to patients treated with warfarin. However, concomitant administration of Cymbalta with warfarin under steady state conditions, in healthy volunteers, as part of a clinical pharmacology study, did not result in a clinically significant change in INR from baseline or in the pharmacokinetics of R- or S-warfarin.

Effects of other medicinal products on Cymbalta
Antacids and H_2 antagonists: Co-administration of Cymbalta with aluminium- and magnesium-containing antacids or Cymbalta with famotidine had no significant effect on the rate or extent of Cymbalta absorption after administration of a 40 mg oral dose.

Inducers of CYP1A2: Population pharmacokinetic analyses have shown that smokers have almost 50% lower plasma concentrations of Cymbalta compared with non-smokers.

4.6 Fertility, pregnancy and lactation

Fertility
In animal studies, Cymbalta had no effect on male fertility, and effects in females were only evident at doses that caused maternal toxicity.

Pregnancy
Studies in animals have shown reproductive toxicity at systemic exposure levels (AUC) of Cymbalta lower than the maximum clinical exposure (see section 5.3).

Two large observational studies do not suggest an overall increased risk of major congenital malformation (one from the US including 2,500 exposed to Cymbalta during the first trimester and one from the EU including 1,500 exposed to Cymbalta during the first trimester). The analysis on specific malformations such as cardiac malformations shows inconclusive results.

In the EU study, maternal exposure to Cymbalta during late pregnancy (at any time from 20 weeks gestational age to delivery) was associated with an increased risk for preterm birth (less than 2-fold, corresponding to approximately 6 additional premature births per 100 women treated with Cymbalta late in pregnancy). The majority occurred between 35 and 36 weeks of gestation. This association was not seen in the US study.

The US observational data have provided evidence of an increased risk (less than 2 fold) of postpartum haemorrhage following duloxetine exposure within the month prior to birth.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). Although no studies have investigated the association of PPHN to SNRIs treatment, this potential risk cannot be ruled out with Cymbalta taking into account the related mechanism of action (inhibition of the re-uptake of serotonin).

As with other serotonergic medicinal products, discontinuation symptoms may occur in the neonate after maternal Cymbalta use near term. Discontinuation symptoms seen with Cymbalta may include hypotonia, tremor, jitteriness, feeding difficulty, respiratory distress and seizures. The majority of cases have occurred either at birth or within a few days of birth.

Cymbalta should be used in pregnancy only if the potential 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.

Lactation
Cymbalta is very weakly excreted into human milk based on a study of 6 lactating patients, who did not breast feed their children. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose (see section 5.2). As the safety of Cymbalta in infants is not known, the use of Cymbalta while breast-feeding is not recommended.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Cymbalta may be associated with sedation and dizziness. Patients should be instructed that if they experience sedation or dizziness they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

The most commonly reported adverse reactions in patients treated with Cymbalta were nausea, headache, dry mouth, somnolence, and dizziness. However, the majority of common adverse reactions were mild to moderate, they usually started early in therapy, and most tended to subside even as therapy was continued.

The table below gives the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials.

Frequency estimate: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Very common	Common	Uncommon	Rare	Very Rare
Infections and infestations				
		Laryngitis		
Immune system disorders				
			Anaphylactic reaction Hyper-sensitivity disorder	
Endocrine disorders				
			Hypo-thyroidism	
Metabolism and nutrition disorders				
	Decreased Appetite	Hyperglycaemia (reported especially in diabetic patients)	Dehydration Hyponatraemia SIADH[6]	
Psychiatric disorders				
	Insomnia Agitation Libido decreased Anxiety Orgasm abnormal Abnormal dreams	Suicidal ideation[5,7] Sleep disorder Bruxism Disorientation Apathy	Suicidal behaviour[5,7] Mania Hallucinations Aggression and anger[4]	
Nervous system disorders				
Headache Somnolence	Dizziness Lethargy Tremor Paraesthesia	Myoclonus Akathisia[7] Nervousness Disturbance in attention Dysgeusia Dyskinesia Restless legs syndrome Poor quality sleep	Serotonin syndrome[6] Convulsion[1] Psychomotor restlessness[6] Extra-pyramidal symptoms[6]	
Eye disorders				
	Blurred vision	Mydriasis Visual impairment	Glaucoma	
Ear and labyrinth disorders				
	Tinnitus[1]	Vertigo Ear pain		
Cardiac disorders				
	Palpitations	Tachycardia Supra-ventricular arrhythmia, mainly atrial fibrillation		
Vascular disorders				
	Blood pressure increase[3] Flushing	Syncope[2] Hypertension[3,7] Orthostatic hypotension[2] Peripheral coldness	Hypertensive crisis[3,6]	
Respiratory, thoracic and mediastinal disorders				
	Yawning	Throat tightness Epistaxis	Interstitial lung disease[10] Eosinophilic pneumonia[6]	
Gastrointestinal disorders				
Nausea Dry mouth	Constipation Diarrhoea Abdominal pain Vomiting Dyspepsia Flatulence	Gastrointestinal haemorrhage[7] Gastroenteritis Eructation Gastritis Dysphagia	Stomatitis Haematochezia Breath odour Microscopic colitis[9]	
Hepato-biliary disorders				
		Hepatitis[3] Elevated liver enzymes (ALT, AST, alkaline phosphatase) Acute liver injury	Hepatic failure[6] Jaundice[6]	
Skin and subcutaneous tissue disorders				
	Sweating increased Rash	Night sweats Urticaria Dermatitis contact Cold sweat Photo-sensitivity reactions Increased tendency to bruise	Stevens-Johnson Syndrome[6] Angio-neurotic oedema[6]	Cutaneous vasculitis
Musculoskeletal and connective tissue disorders				
	Musculo-skeletal pain Muscle spasm	Muscle tightness Muscle twitching	Trismus	
Renal and urinary disorders				
	Dysuria Pollakiuria	Urinary retention Urinary hesitation Nocturia Polyuria Urine flow decreased	Urine odour abnormal	
Reproductive system and breast disorders				
	Erectile dysfunction Ejaculation disorder Ejaculation delayed	Gynaecological haemorrhage Menstrual disorder Sexual dysfunction Testicular pain	Menopausal symptoms Galactorrhoea Hyperprolactinaemia Postpartum haemorrhage[6]	
General disorders and administration site conditions				
	Falls[8] Fatigue	Chest pain[7] Feeling abnormal Feeling cold Thirst Chills Malaise Feeling hot Gait disturbance		
Investigations				
	Weight decrease	Weight increase Blood creatine phosphokinase increased Blood potassium increased	Blood cholesterol increased	

1 Cases of convulsion and cases of tinnitus have also been reported after treatment discontinuation.
2 Cases of orthostatic hypotension and syncope have been reported especially at the initiation of treatment.
3 See section 4.4.
4 Cases of aggression and anger have been reported particularly early in treatment or after treatment discontinuation.
5 Cases of suicidal ideation and suicidal behaviours have been reported during Cymbalta therapy or early after treatment discontinuation (see section 4.4).
6 Estimated frequency of post-marketing surveillance reported adverse reactions; not observed in placebo-controlled clinical trials.
7 Not statistically significantly different from placebo.
8 Falls were more common in the elderly (≥65 years old).
9 Estimated frequency based on all clinical trial data.
10 Estimated frequency based on placebo-controlled clinical trials.

Description of selected adverse reactions
Discontinuation of Cymbalta (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia or electric shock-like sensations, particularly in the head), sleep disturbances (including insomnia and intense dreams), fatigue, somnolence, agitation or anxiety, nausea and/or vomiting, tremor, headache, myalgia, irritability, diarrhoea, hyperhydrosis and vertigo are the most commonly reported reactions.

Generally, for SSRIs and SNRIs, these events are mild to moderate and self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when Cymbalta treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

In the 12 week acute phase of three clinical trials of Cymbalta in patients with diabetic peripheral neuropathic pain, small but statistically significant increases in fasting blood glucose were observed in Cymbalta-treated patients. HbA1c was stable in both Cymbalta-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 Cymbalta and routine care groups, but the mean increase was 0.3% greater in the Cymbalta-treated group. There was also a small increase in fasting blood glucose and in total cholesterol in Cymbalta-treated patients while those laboratory tests showed a slight decrease in the routine care group.

The heart rate-corrected QT interval in Cymbalta-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, QRS, or QTcB measurements between Cymbalta-treated and placebo-treated patients.

4.9 Overdose

Cases of overdoses, alone or in combination with other medicinal products, with Cymbalta doses of 5400 mg were reported. Some fatalities have occurred, primarily with mixed overdoses, but also with Cymbalta alone at a dose of approximately 1000 mg. Signs and symptoms of overdose (Cymbalta alone or in combination with other medicinal products) included somnolence, coma, serotonin syndrome, seizures, vomiting and tachycardia.

No specific antidote is known for Cymbalta but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. A free 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. Cymbalta has a large volume of distribution and forced diuresis, haemoperfusion, and exchange perfusion are unlikely to be beneficial.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants. ATC code: N06AX21.

Mechanism of action
Cymbalta 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. Cymbalta dose-dependently increases extracellular levels of serotonin and noradrenaline in various brain areas of animals.

Pharmacodynamic effects
Cymbalta normalised pain thresholds in several preclinical models of neuropathic and inflammatory pain and attenuated pain behaviour in a model of persistent pain. The pain inhibitory action of Cymbalta is believed to be a result of potentiation of descending inhibitory pain pathways within the central nervous system.

Clinical efficacy and safety
Major Depressive Disorder: Cymbalta was studied in a clinical programme involving 3,158 patients (1,285 patient-years of exposure) meeting DSM-IV criteria for major depression. The efficacy of Cymbalta at the recommended dose of 60 mg once a day was demonstrated in three out of three randomised, double-blind, placebo-controlled, fixed dose acute studies in adult outpatients with major depressive disorder. Overall, Cymbalta's efficacy has been demonstrated at daily doses between 60 and 120 mg in a total of five out of seven randomised, double-blind, placebo-controlled, fixed dose acute studies in adult outpatients with major depressive disorder.

Cymbalta demonstrated statistical superiority over placebo as measured by improvement in the 17-item Hamilton Depression Rating Scale (HAM-D) total score (including both the emotional and somatic symptoms of depression). Response and remission rates were also statistically significantly higher with Cymbalta compared with placebo. Only a small proportion of patients included in pivotal clinical trials had severe depression (baseline HAM-D>25).

In a relapse prevention study, patients responding to 12-weeks of acute treatment with open-label Cymbalta 60 mg once daily were randomised to either Cymbalta 60 mg once daily or placebo for a further 6-months. Cymbalta 60 mg once daily demonstrated a statistically significant superiority compared to placebo (p=0.004) on the primary outcome measure, the prevention of depressive relapse, as measured by time to relapse. The incidence of relapse during the 6-months double-blind follow-up period was 17% and 29% for Cymbalta and placebo, respectively.

During 52 weeks of placebo-controlled double blind treatment, Cymbalta-treated patients with recurrent major depressive disorder had a significantly longer symptom free period (p<0.001) compared with patients randomised to placebo. All patients had previously responded to Cymbalta during open-label Cymbalta treatment (28 to 34 weeks) at a dose of 60 to 120 mg/day. During the 52-week placebo-controlled double blind treatment phase 14.4% of the Cymbalta-treated patients and 33.1% of the placebo-treated patients experience a return of their depressive symptoms (p<0.001).

The effect of Cymbalta 60 mg once a day in elderly depressed patients (≥65 years) was specifically examined in a study that showed a statistically significant difference in the reduction of the HAM-D17 score for Cymbalta-treated patients compared to placebo. Tolerability of Cymbalta 60 mg once daily in elderly patients was comparable to that seen in the younger adults. However, data on elderly patients exposed to the maximum dose (120mg per day) are limited and thus, caution is recommended when treating this population.

Generalised Anxiety Disorder: Cymbalta demonstrated statistically significant superiority over placebo in five out of five studies including four randomised, double-blind, placebo-controlled acute studies and a relapse prevention study in adult patients with generalised anxiety disorder.

Cymbalta demonstrated statistically significant superiority over placebo as measured by improvement in the Hamilton Anxiety Scale (HAM-A) total score and by the Sheehan Disability Scale (SDS) global functional impairment score. Response and remission rates were also higher with Cymbalta compared to placebo. Cymbalta showed comparable efficacy results to venlafaxine in terms of improvements on the HAM-A total score.

In a relapse prevention study, patients responding to 6 months of acute treatment with open-label Cymbalta were randomised to either Cymbalta or placebo for a further 6-months. Cymbalta 60 mg to 120 mg once daily demonstrated statistically significant superiority compared to placebo (p<0.001) on the prevention of relapse, as measured by time to relapse. The incidence of relapse during the 6-months double-blind follow-up period was 14% for Cymbalta and 42% for placebo.

The efficacy of Cymbalta 30-120 mg (flexible dosing) once a day in elderly patients (> 65 years) with generalised anxiety disorder was evaluated in a study that demonstrated statistically significant improvement in the HAM-A total score for Cymbalta-treated patients compared to placebo-treated patients. The efficacy and safety of Cymbalta 30-120 mg once daily in elderly patients with generalised anxiety disorder was similar to that seen in studies of younger adult patients. However, data on elderly patients exposed to the maximum dose (120 mg per day) are limited and, thus, caution is recommended when using this dose with the elderly population.

Diabetic Peripheral Neuropathic Pain: The efficacy of Cymbalta as a treatment for diabetic peripheral neuropathic pain was established in 2 randomised, 12-weeks, double-blind, placebo-controlled, fixed dose studies in adults (22 to 88 years) having diabetic peripheral neuropathic pain for at least 6 months. Patients meeting diagnostic criteria for major depressive disorder were excluded from these trials. The primary outcome measure was the weekly mean of 24-hour average pain, which was collected in a daily diary by patients on an 11-point Likert scale.

In both studies, Cymbalta 60 mg once daily and 60 mg twice daily significantly reduced pain compared with placebo. The effect in some patients was apparent in the first week of treatment. The difference in mean improvement between the two active treatment arms was not significant. At least 30% reported pain reduction was recorded in approximately 65% of Cymbalta-treated patients versus 40% for placebo. The corresponding figures for at least 50% pain reduction were 50% and 26% respectively. Clinical response rates (50% or greater improvement in pain) were analysed according to whether or not the patient experienced somnolence during treatment. For patients not experiencing somnolence, clinical response was observed in 47% of patients receiving Cymbalta and 27% of patients on placebo. Clinical response rates in patients experiencing somnolence were 60% on Cymbalta and 30% on placebo. Patients not demonstrating a pain reduction of 30% within 60 days of treatment were unlikely to reach this level during further treatment.

In an open label long-term uncontrolled study, the pain reduction in patients responding to 8-weeks of acute treatment of Cymbalta 60 mg once daily was maintained for a further 6-months as measured by change on the Brief Pain Inventory (BPI) 24-hour average pain item.

Fibromyalgia: The efficacy of Cymbalta was demonstrated in 2 randomised, double-blind, placebo-controlled studies in adult patients with fibromyalgia with or without depression meeting the American College of Rheumatology criteria for fibromyalgia.

In a 3-month study, Cymbalta 60 mg once daily and 60 mg twice daily demonstrated statistical superiority over placebo as measured by improvement on the Brief Pain Inventory (BPI) average pain score. In a 6-month study Cymbalta 60 mg once daily and 120 mg once daily demonstrated statistical superiority over placebo at both 3 and 6 months as measured by improvement in the BPI average pain score. In both studies the pain reduction was apparent after 1 week of treatment. Using pooled data from the two studies at 3 months, approximately 53% of Cymbalta-treated patients versus 27% of placebo treated patients recorded clinically relevant pain relief measured as at least 30% pain reduction. The corresponding figures for at least 50% pain reduction were 39% and 23% respectively. The improvement was irrespective of presence or absence of depression, and depression symptoms, as measured by the HAM-D17, also significantly improved. Confirmation of the clinical relevance of the pain reduction was shown by statistical superiority over placebo in overall patient wellbeing as measured by the Patient rated Global Impression of Improvement (PGI-I) score.

Patients also demonstrated statistically significant improvements compared with placebo in clinician rated overall improvement as measured by the Clinical Global Impression (CGI) Severity Scale, pain interference as measured by the BPI Average Interference score, functioning as measured by the Fibromyalgia Impact Questionnaire (FIQ total score) and mental fatigue as measured by the Multidimensional Fatigue Inventory (MFI) Mental Fatigue Domain.

In a long-term uncontrolled study the safety profile and initial improvement in the BPI average pain score observed after 8 weeks of treatment was maintained for up to one additional year.

A single study has been performed in paediatric patients with juvenile primary fibromyalgia syndrome (JPFS) in which the Cymbalta-treated group did not separate from placebo group for the primary efficacy measure. Therefore, there is no evidence of efficacy in this paediatric patient population. The randomised, double-blind, placebo-controlled, parallel study of Cymbalta was conducted in 184 adolescents aged 13 to 18 years (mean age 15.53 years) with JPFS. The study included a 13-weekdouble-blind period where patients were randomised to Cymbalta 30 mg/60 mg, or placebo daily. Cymbalta did not show efficacy in reducing pain as measured by primary outcome measure of Brief Pain Inventory (BPI) average pain score endpoint: least squares (LS) mean change from baseline in BPI average pain score at 13 weeks was -0.97 in the placebo group, compared with -1.62 in the Cymbalta 30/60 mg group (p = 0.052). The safety results from this study were consistent with the known safety profile of Cymbalta.

5.2 Pharmacokinetic properties

Cymbalta is administered as a single enantiomer. Cymbalta is extensively metabolised by oxidative enzymes (CYP1A2 and the polymorphic CYP2D6), followed by conjugation. The pharmacokinetics of Cymbalta demonstrate large intersubject variability (generally 50-60%), partly due to gender, age, smoking status and CYP2D6 metaboliser status.

Absorption: Cymbalta is well absorbed after oral administration with a C_{max} occurring 6 hours post dose. The absolute oral bioavailability of Cymbalta ranged from 32 to 80% (mean of 50%). Food delays the time to reach the peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11 %). These changes do not have any clinical significance.

Distribution: Cymbalta is approximately 96% bound to human plasma proteins. Cymbalta binds to both albumin and alpha-l acid glycoprotein. Protein binding is not affected by renal or hepatic impairment.

Biotransformation: Cymbalta is extensively metabolised and the metabolites are excreted principally in urine. Both cytochromes P450-2D6 and 1A2 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 Cymbalta are considered pharmacologically inactive. The pharmacokinetics of Cymbalta in patients who are poor metabolisers with respect to CYP2D6 has not been specifically investigated. Limited data suggest that the plasma levels of Cymbalta are higher in these patients.

Elimination: The elimination half-life of Cymbalta ranges from 8 to 17 hours (mean of 12 hours). After an intravenous dose the plasma clearance of Cymbalta ranges from 22 to 46 l/hr (mean of 36 l/hr). After an oral dose the apparent plasma clearance of Cymbalta ranges from 33 to 261 l/hr (mean 101 l/hr).

Gender: Pharmacokinetic differences have been identified between males and females (apparent plasma clearance is approximately 50% lower in females). Based upon the overlap in the range of clearance, gender-based pharmacokinetic differences do not justify the recommendation for using a lower dose for female patients.

Age: Pharmacokinetic differences have been identified between younger and elderly females (≥65 years) (AUC increases by about 25% and half-life is about 25% longer in the elderly), although the magnitude of these changes is not sufficient to justify adjustments to the dose. As a general recommendation, caution should be exercised when treating the elderly (see sections 4.2 and 4.4).

Renal impairment: End stage renal disease (ESRD) patients receiving dialysis had 2-fold higher Cymbalta C_{max} and AUC values compared with healthy subjects. Pharmacokinetic data on Cymbalta is limited in patients with mild or moderate renal impairment.

Hepatic impairment: Moderate liver disease (Child Pugh Class B) affected the pharmacokinetics of Cymbalta. Compared with healthy subjects, the apparent plasma clearance of Cymbalta was 79% lower, the apparent terminal half-life was 2.3 times longer, and the AUC was 3.7 times higher in patients with moderate liver disease. The pharmacokinetics of Cymbalta and its metabolites have not been studied in patients with mild or severe hepatic insufficiency.

Breast-feeding mothers: The disposition of Cymbalta was studied in 6 lactating women who were at least 12-weeks postpartum. Cymbalta is detected in breast milk, and steady-state concentrations in breast milk are about one-fourth those in plasma. The amount of Cymbalta in breast milk is approximately 7 µg/day while on 40 mg twice daily dosing. Lactation did not influence Cymbalta pharmacokinetics.

5.3 Preclinical safety data

Cymbalta was not genotoxic in a standard battery of tests and was not carcinogenic in rats. Multinucleated cells were seen in the liver in the absence of other histopathological changes in the rat carcinogenicity study. The underlying mechanism and the clinical relevance are unknown. Female mice receiving Cymbalta 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 microsomal enzyme induction. The relevance of this mouse data to humans is unknown. Female rats receiving Cymbalta (45 mg/kg/day) before and during mating and early pregnancy had a decrease in maternal food consumption and body weight, oestrous cycle disruption, decreased live birth indices and progeny survival, and progeny growth retardation at systemic exposure levels estimated to be at the most at maximum clinical exposure (AUC). In an embryotoxicity study in the rabbit, a higher incidence of cardiovascular and skeletal malformations was observed at systemic exposure levels below the maximum clinical exposure (AUC). No malformations were observed in another study testing a higher dose of a different salt of duloxetine. In prenatal/postnatal toxicity studies in the rat, Cymbalta induced adverse behavioural effects in the offspring at exposures below maximum clinical exposure (AUC).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Hypromellose, hydroxypropyl methylcellulose acetate succinate, sucrose, sugar spheres, talc, titanium dioxide (E171), triethyl citrate.

Capsule shell:
30 mg: Gelatin, sodium lauryl sulfate, titanium dioxide (E171), indigo carmine (E132), edible green ink.

Edible green ink contains: Black iron oxide - synthetic (E172), yellow iron oxide - synthetic (E172), propylene glycol, shellac.

60mg: Gelatin, sodium lauryl sulphate, titanium dioxide (E171), indigo carmine (E132), yellow iron oxide (E172), edible white ink.

Edible white ink contains: titanium dioxide (E171), propylene glycol, shellac, povidone.

6.2 Special precautions for storage

Store in the original package in order to protect from moisture. Do not store above 30ºC.

6.3 Presentation

Available in packs of 14 and 28 capsules. Not all pack sizes may be marketed.

7. PRODUCT OWNER

Eli Lilly and Company, Indianapolis, Indiana 46285, US

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CYMBALTA
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