1. NAME OF THE MEDICINAL PRODUCT

CYMBALTA

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The acive ingredient in CYMBALTA is duloxetine.
Each capsule contains 30 mg or 60 mg of duloxetine as hydrochloride

Excipients:
Each 30mg capsule contains 8.6 mg sucrose.
Each 60mg capsule contains 17.2 mg sucrose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gastro-resistant capsule.

The CYMBALTA 30mg capsule has an opaque white body, imprinted with “30mg” and an opaque blue cap, imprinted with “9543”

The CYMBALTA 60mg capsule has an opaque green body, imprinted with “60mg” and an opaque blue cap, imprinted with “9542”

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cymbalta is indicated for the treatment of major depressive episodes (MDD).

Cymbalta is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPNP).

Cymbalta is indicated for the treatment of generalized anxiety disorder (GAD).

Cymbalta is indicated for the management of fibromyalgia (FM) .

4.2 Posology and method of administration

For oral use.

Adults
Major Depressive Episodes:
The starting and recommended maintenance dose is 60 mg once daily with or without food. Dosages above 60 mg once daily, up to a maximum dose of 120 mg per day 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.

Diabetic Peripheral Neuropathic Pain:
The starting and recommended maintenance dose is 60 mg daily with or without food. Dosages above 60 mg once daily, up to a maximum dose of 120 mg per day administered in evenly divided doses, have been evaluated from a safety perspective in clinical trials. The plasma concentration of duloxetine displays large

inter-individual variability (see 5.2). Hence, some patients that respond insufficiently to 60 mg may benefit from a higher dose.

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. 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 5.1).

Generalized Anxiety Disorder
For most patients, the recommended starting dose for Cymbalta is 60 mg administered once daily without regard to meals. 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.
Generalized anxiety disorder is generally recognized as a chronic condition. The effectiveness of Cymbalta in long-term use for GAD, that is, for more than 10 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use Cymbalta for extended periods should periodically evaluate the long-term usefulness of the drug for the individual patient.

Fibromyalgia
The recommended dose for Cymbalta is 60 mg administered once daily. Treatment should begin at 30 mg once daily for 1 week, to allow patients to adjust to the medication before increasing to 60 mg once daily. Some patients may respond to the starting dose. There is no 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 .
Fibromyalgia is recognized as a chronic condition. 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.[1]

Elderly
No dosage adjustment is recommended for elderly patients solely on the basis of age. As with any drug, caution should be exercised when treating the elderly. When individualizing the dosage in elderly patients, extra care should be taken when increasing the dose [1](see sections 4.4 and 5.2)

Children and adolescents
The safety and efficacy of duloxetine in these age groups have not been studied. Therefore, administration of CYMBALTA to children and adolescents is not recommended (see section 4.4).

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). CYMBALTA must not be used in patients with severe renal impairment (creatinine clearance <30 ml/min; see section 4.3).

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 the active substance or to any of the excipients.

Concomitant use of CYMBALTA with nonselective, irreversible Monoamine Oxidase Inhibitors (MAOIs) is contraindicated (see section 4.5).

Liver disease resulting in hepatic impairment (see section 5.2).

CYMBALTA should not be used in combination with fluvoxamine, ciprofloxacin or enoxacine (i.e. potent CYP1A2 inhibitors) since the combination results in elevated plasma concentrations of duloxetine (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 duloxetine, 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
Duloxetine 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 duloxetine. Cases of hypertensive crisis have been reported with duloxetine, 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. Duloxetine should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure. Caution should also be exercised when duloxetine 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 duloxetine either dose reduction or gradual discontinuation should be considered (see section 4.8). In patients with uncontrolled hypertension duloxetine should not be initiated (see section 4.3).

Renal impairment
Increased plasma concentrations of duloxetine 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 or Neuroleptic Malignant Syndrome (NMS)-like Reactions
The development of a potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs alone, including CYMBALTA treatment, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

The concomitant use of Cymbalta with MAOIs intended to treat depression is contraindicated [see Contraindications (4.3) and Drug Interactions (4.5)].

If concomitant treatment of Cymbalta with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases [see Drug Interactions (4.5)].

The concomitant use of Cymbalta with serotonin precursors (such as tryptophan) is not recommended [see Drug Interactions (4.5)].

Treatment with duloxetine and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above reactions occur and supportive symptomatic treatment should be initiated.

Use with antidepressants
Caution should be exercised when using CYMBALTA in combination with antidepressants. In particular the combination with selective reversible MAOIs is not recommended.

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
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.[2]
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 duloxetine therapy or early after treatment discontinuation (see section 4.8). Close supervision of patients and in particular those at high risk should accompany drug 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.

Use in children and adolescents under 18 years of age
No clinical trials have been conducted with duloxetine in paediatric populations. 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. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Haemorrhage
There have been reports of bleeding abnormalities, such as ecchymoses purpura and gastrointestinal haemorrhage with selective serotonin reuptake inhibitors (SSRIs) and serotonin/ noradrenaline reuptake inhibitors (SNRIs). Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function, and in patients with known bleeding tendencies.

Hyponatraemia
Hyponatraemia has been reported 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).

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 SSRI's and SNRI's 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 duloxetine 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
Of the 2,418 patients in premarketing clinical studies of Cymbalta for MDD, 5.9% (143) were 65 years of age or over. Of the 1,074 patients in the DPNP premarketing studies, 33% (357) were 65 years of age or over. Of the 1,761 patients in FM premarketing studies, 7.9% (140) were 65 years of age or over. Premarketing clinical studies of GAD did not include sufficient numbers of subjects age 65 or over to determine whether they respond differently from younger subjects. In the MDD, DPNP, and FM studies, 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, but greater sensitivity of some older individuals cannot be ruled out. SSRIs and SNRIs, including Cymbalta have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event.

Akathisia/psychomotor restlessness
The use of duloxetine 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 neuropathic pain, major depressive episodes, generalized anxiety disorder, fibromyalgia as well as 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 duloxetine (see section 4.8). Most of them occurred during the first months of treatment. The pattern of liver damage was predominantly hepatocellular. Duloxetine should be used with caution in patients treated with other medicinal products associated with hepatic injury. Cymbalta should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established.

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

4.5 Interaction with other medicinal products and other forms of interaction

CNS medicinal products: the risk of using duloxetine 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 and substances including alcohol and sedative medicinal products (e.g. benzodiazepines, morphinomimetics, antipsychotics, phenobarbital, sedative antihistamines).

Monoamine Oxidase Inhibitors (MAOIs): due to the risk of serotonin syndrome, duloxetine should not be used in combination with nonselective irreversible 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 (see section 4.3).

For selective, reversible MAOIs, like moclobemide, the risk of serotonin syndrome is lower. However, the concomitant use of CYMBALTA with selective, reversible MAOIs is not recommended (see section 4.4).

Serotonin syndrome: in rare cases, serotonin syndrome has been reported in patients using SSRIs (e.g. paroxetine, fluoxetine)or SNRIs 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.
A combination of symptoms, such as agitation, tremor, myoclonus and hyperthermia may indicate the development of this condition. If this occurs treatment with the SSRI/SNRI and the serotonergic medicinal product should be discontinued immediately and symptomatic tretament initiated.

Effect of duloxetine on other medicinal products
Medicinal products metabolised by CYP1A2: The pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by co-administration with duloxetine (60 mg twice daily).

Medicinal products 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 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, tricyclic antidepressants (TCAs) such as nortriptyline, amitriptyline, and imipramine) particularly if they have a narrow therapeutic index (such as flecainide, propafenone and metoprolol).

Oral contraceptives and other steroidal agents: results of *in vitro* studies demonstrate that duloxetine 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 duloxetine 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 duloxetine was co-administered to patients treated with warfarin. However, concomitant administration of duloxetine 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 duloxetine
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.

Inhibitors of CYP 1A2: because CYP1A2 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP1A2 is likely to result in higher concentrations of duloxetine. Fluvoxamine (100 mg once daily), a potent inhibitor of CYP1A2, decreased the apparent plasma clearance of duloxetine 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).

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

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data on the use of duloxetine in pregnant women. Studies in animals have shown reproductive toxicity at systemic exposure levels (AUC) of duloxetine lower than the maximum clinical exposure (see section 5.3).
The potential risk for humans is unknown. As with other serotonergic medicinal products, discontinuation symptoms may occur in the neonate after maternal duloxetine use near term. 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.

Breast feeding
Duloxetine 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 duloxetine 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

Table 1 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials,(comprising a total of 8239 patients, 5075 on duloxetine and 3164 on placebo) in depression, generalized anxiety disorder, diabetic neuropathic pain and fibromyalgia.

The most commonly reported adverse reactions in patients treated with CYMBALTA were nausea, headache, dry mouth, somnolence, fatigue, insomnia, dizziness and constipation. 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.

Table 1: Adverse reactions
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), not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Very common	Common	Uncommon	Rare	Very Rare	Frequency not known
Infections and infestations					
		Laryngitis			
Immune system disorders					
			Anaphylactic reaction Hyper-sensitivity disorder		
Endocrine disorders					
			Hypo-thyroidism		
Metabolism and Nutrition Disorders					
	Decreased Appetite	Hyperglycemia (reported especially in diabetic patients)	Dehydration Hyponatremia		SIADH
Psychiatric Disorders					
	Insomnia Agitation Libido decreased Anxiety Orgasm	Sleep disorder Bruxism Disorientation Apathy	Mania Hallucinations Aggression and anger[4]		Suicidal ideation [5] Suicidal[5] behaviour

Very common	Common	Uncommon	Rare	Very Rare	Frequency not known
	abnormal Abnormal dreams				
Nervous System Disorders					
Headache (14.3%) Somnolence (10.7%) Dizziness (10.2%)	Tremor Paraesthesia	Myoclonus Nervousness Disturbance in attention Lethargy Dysgeusia Dyskinesia Restless legs syndrome Poor quality sleep	Convulsion[1]		Serotonin syndrome Extra-pyramidal symptoms Akathisia Psychomotor restlessness
Eye Disorders					
	Blurred vision	Mydriasis Visual disturbance	Glaucoma		
Ear and Labyrinth Disorders					
	Tinnitus[1]	Vertigo Ear pain			
Cardiac Disorders					
	Palpitations	Tachycardia Supra-ventricular arrhythmia, mainly atrial fibrillation			
Vascular Disorders					
	Flushing	Blood pressure increase Peripheral coldness Orthostatic hypotension[2] Syncope[2]			Hypertension Hypertensive crisis
Respiratory, thoracic and mediastinal disorders					
	Yawning	Throat tightness Epistaxis			
Gastrointestinal Disorders					
Nausea (24.3%) Dry mouth (12.8%)	Constipation Diarrhoea Vomiting Dyspepsia Flatulence	Gastroenteritis Eructation Gastritis	Stomatitis Breath odour Haematochezia		Gastrointestinal haemorrhage
Hepato-biliary disorders					
		Elevated liver enzymes (ALT,			Jaundice Hepatic

Very common	Common	Uncommon	Rare	Very Rare	Frequency not known
		AST, alkaline phosphatase) Hepatitis[3] Acute liver injury			failure
Skin and Subcutaneous Tissue Disorders					
	Sweating increased Rash	Night sweats Urticaria Dermatitis contact Cold sweat Photo-sensitivity reactions Increased tendency to bruise			Angio-neurotic oedema Stevens-Johnson Syndrome
Muscoloskeletal and connective tissue disorders					
	Musculo-skeletal pain Muscle tightness Muscle spasm	Muscle twitching	Trismus		
Renal and Urinary Disorders					
		Urinary Retention Dysuria Urinary hesitation Nocturia Polyuria Urine flow decreased	Urine odour abnormal		
Reproductive System and Breast Disorders					
	Erectile dysfunction	Ejaculation disorder Ejaculation delayed Sexual dysfunction Gynaecological haemorrhage	Menopausal symptoms		
General Disorders and Administration Site Conditions					
	Fatigue Abdominal pain	Feeling abnormal Feeling cold Thirst Chills Malaise Feeling hot Gait disturbance			Chest pain

Very common	Common	Uncommon	Rare	Very Rare	Frequency not known
Investigations					
	Weight decrease	Weight increase Creatine phosphokinase 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 of after treatment discontinuation.

[5]Cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation (see section 4.4).

Discontinuation of duloxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), fatigue. agitation or anxiety, nausea and/or vomiting, tremor, headache 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 duloxetine 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 duloxetine in patients with diabetic neuropathic pain, small but statistically significant 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 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.

The heart rate-corrected QT interval in duloxetine-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 duloxetine-treated and placebo-treated patients.

4.9 Overdose

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

No specific antidote is known for duloxetine 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. Duloxetine 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.

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 increases extracellular levels of serotonin and noradrenaline in various brain areas of animals.

Duloxetine 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 duloxetine is believed to be a result of potentiation of descending inhibitory pain pathways within the central nervous system.

Major Depressive Episodes:
CYMBALTA was studied in a clinical programme involving 3158 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 randomized, 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 randomized, 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 duloxetine and placebo, respectively.

The effect of CYMBALTA 60 mg once a day in elderly depressed patients ($\geq$65 years) was specifically examined in a study that showed a statistically significative difference in the reduction of the HAMD17 score for duloxetine-treated patients compared to placebo. Tolerability of CYMBALTA 60 mg once day 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.

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. Study 1 and 2 enrolled a total of 791 patients of whom 592 (75%) completed the studies. Patients enrolled 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). Patients were permitted up to 4 g of acetaminophen per day as needed for pain, in addition to CYMBALTA. Patients recorded their pain daily in a diary.

Both studies compared CYMBALTA 60 mg once daily or 60 mg twice daily with placebo. Study 1 additionally compared CYMBALTA 20 mg with placebo. A total of 457 patients (342 Cymbalta, 115 placebo) were enrolled in Study 1 and a total of 334 patients (226 Cymbalta, 108 placebo) were enrolled in Study 2. 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.

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 of the Brief Pain Inventory (BPI) 24-hour average pain item.

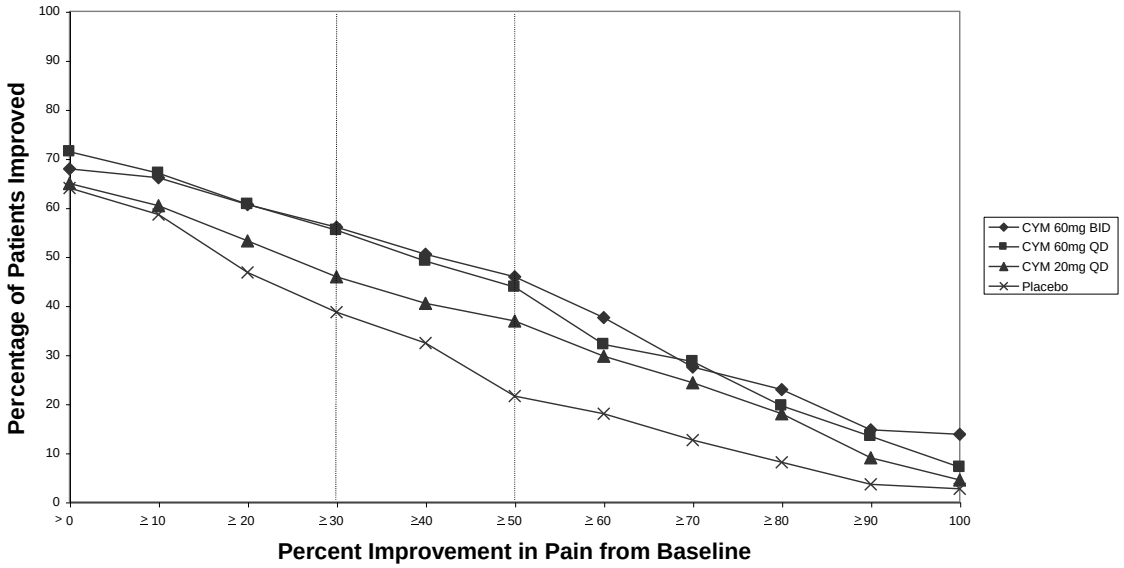

Figure 1: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity - Study 1

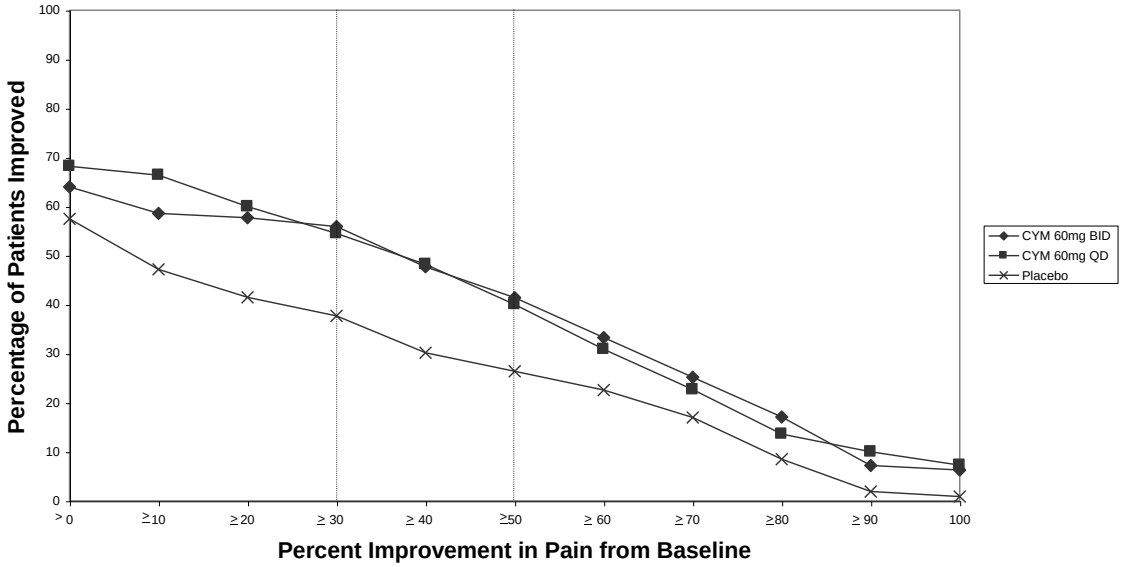

Figure 2: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity - Study 2

Generalized Anxiety Disorder

Generalized anxiety disorder is defined by the DSM-IV as excessive anxiety and worry, present more days than not, for at least 6 months. The excessive anxiety and worry must be difficult to control and must cause significant distress or impairment in normal functioning. It must be associated with at least 3 of the following 6 symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and/or sleep disturbance.

The efficacy of Cymbalta has been established in three 9- or 10-week placebo-controlled trials of outpatients who met DSM-IV diagnostic criteria for generalized anxiety disorder.
The efficacy of Cymbalta in the treatment of generalized anxiety disorder (GAD) was established in 1 fixed-dose randomized, double-blind, placebo-controlled trial and 2 flexible-dose randomized, double-blind, placebo-controlled trials in adult outpatients between 18 and 83 years of age meeting the DSM-IV criteria for GAD.
In 1 flexible-dose study and in the fixed-dose study, the starting dose was 60 mg once daily where down titration to 30 mg once daily was allowed for tolerability reasons before increasing it to 60 mg once daily. Fifteen percent of patients were down titrated. One flexible-dose study had a starting dose of 30 mg once daily for 1 week before increasing it to 60 mg once daily.
The 2 flexible-dose studies involved dose titration with Cymbalta doses ranging from 60 mg once daily to 120 mg once daily (N=168 and N=162) compared to placebo (N=159 and N=161) over a 10-week treatment period. The mean dose for completers at endpoint in the flexible-dose studies was 104.75 mg/day. The fixed-dose study evaluated Cymbalta doses of 60 mg once daily (N=168) and 120 mg once daily (N=170) compared to placebo (N=175) over a 9-week treatment period. While a 120 mg/day dose was shown to be effective, there is no evidence that doses greater than 60 mg/day confer additional benefit.
In all 3 studies, Cymbalta demonstrated superiority over placebo as measured by greater improvement in the Hamilton Anxiety Scale (HAM-A) total score and by the Sheehan Disability Scale (SDS) global functional impairment score. The SDS is a widely used and well-validated scale that measures the extent emotional symptoms disrupt patient functioning in 3 life domains: work/school, social life/leisure activities and family life/home responsibilities.
Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.
The effectiveness of Cymbalta in long-term use for GAD, that is, for more than 10 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use Cymbalta for extended periods should periodically evaluate the long-term usefulness of the drug for the individual patient.

Fibromyalgia
The efficacy of Cymbalta for the management of fibromyalgia was established in two randomized, double-blind, placebo-controlled, fixed-dose studies in adult patients meeting the American College of Rheumatology criteria for fibromyalgia (a history of widespread pain for 3 months, and pain present at 11 or more of the 18 specific tender point sites). Study 1 was three months in duration and enrolled female patients only. Study 2 was six months in duration and enrolled male and female patients. Approximately 25% of participants had a comorbid diagnosis of major depressive disorder (MDD). Study 1 and 2 enrolled a total of 874 patients of whom 541 (62%) completed the studies. The patients had a baseline pain score of 6.5 on an 11-point scale ranging from 0 (no pain) to 10 (worse possible pain).
Both studies compared Cymbalta 60 mg once daily or 120 mg daily (given in divided doses in Study 1 and as a single daily dose in Study 2) with placebo. Study 2 additionally compared Cymbalta 20 mg with placebo during the initial three months of a six-month study. A total of 354 patients (234 Cymbalta, 120 placebo) were enrolled in Study 1 and a total of 520 patients (376 Cymbalta, 144 placebo) were enrolled in Study 2 (5% male, 95% female). Treatment with Cymbalta 60 mg or 120 mg daily statistically significantly improved the endpoint mean pain scores from baseline and increase the proportion of patients with at least a 50% reduction in pain score from baseline. Pain reduction was observed in patients both with and without comorbid MDD. However, the degree of pain reduction may be greater in patients with comorbid MDD. For various degrees of improvement in pain from baseline to study endpoint, Figures 3 and 4 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. Improvement was also demonstrated on measures of function (Fibromyalgia Impact Questionnaires) and patient global impression of change (PGI). Neither study demonstrated a benefit of 120 mg compared to 60 mg, and a higher dose was associated with more adverse reactions and premature discontinuations of treatment.

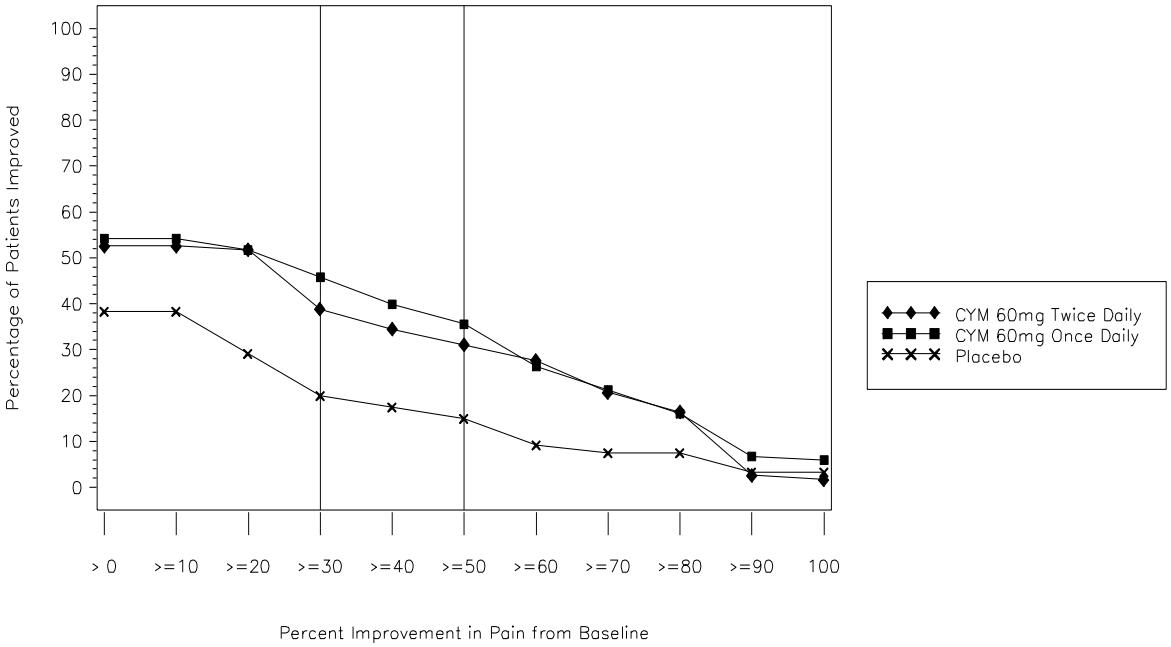

Figure 3: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity - Study 1

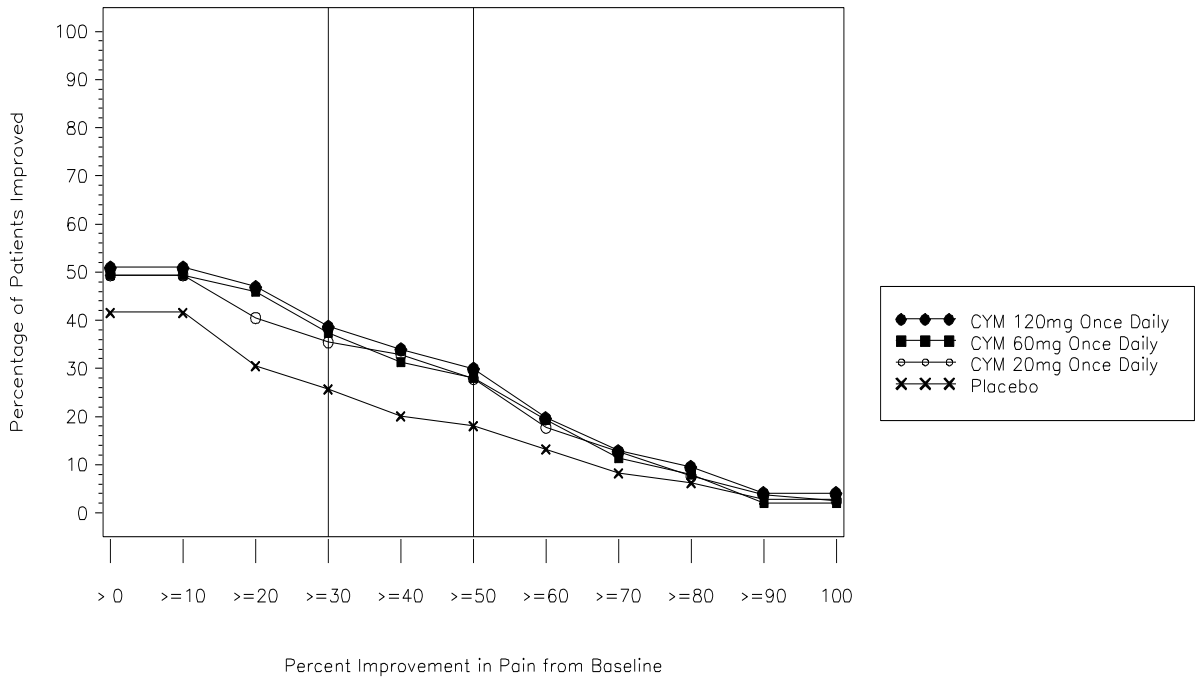

Figure 4: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity - Study 2

Additionally, the benefit of up-titration in non-responders to Cymbalta at 60 mg/day was evaluated in a separate study. Patients were initially treated with Cymbalta 60 mg once daily for eight weeks in open-label fashion. Subsequently, completers of this phase were randomized to double-blind treatment with Cymbalta at either 60 mg once daily or 120 mg once daily. Those patients who were considered non-responders, where response was defined as at least a 30% reduction in pain score from baseline at the end of the 8-week treatment, were no more likely to meet response criteria at the end of 60 weeks of treatment if blindly titrated to Cymbalta 120 mg as compared to those who were blindly continued on Cymbalta 60 mg.

5.2 Pharmacokinetic properties

Duloxetine is administered as a single enantiomer. Duloxetine is extensively metabolised by oxidative enzymes (CYP1A2 and the polymorphic CYP2D6), followed by conjugation. The pharmacokinetics of duloxetine demonstrate large intersubject variability (generally 50-60%), partly due to gender, age, smoking status and CYP2D6 metaboliser status.
Absorption: Duloxetine is well absorbed after oral administration with a Cmax occurring 6 hours post dose. The absolute oral bioavailability of duloxetine 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: Duloxetine is approximately 96% bound to human plasma proteins. Duloxetine binds to both albumin and alpha-l acid glycoprotein. Protein binding is not affected by renal or hepatic impairment.

Biotransformation: Duloxetine 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 duloxetine are considered pharmacologically inactive. The pharmacokinetics of duloxetine in patients who are poor metabolisers with respect to CYP2D6 has not been specifically investigated. Limited data suggest that the plasma levels of duloxetine are higher in these patients.

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

Special populations:
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 duloxetine Cmax and AUC values compared with healthy subjects. Pharmacokinetic data on duloxetine is limited in patients with mild or moderate renal impairment.

Hepatic impairment: moderate liver disease (Child Pugh Class B) affected the pharmacokinetics of duloxetine. Compared with healthy subjects, the apparent plasma clearance of duloxetine 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 duloxetine and its metabolites have not been studied in patients with mild or severe hepatic insufficiency.

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

5.3 Preclinical safety data

Duloxetine 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 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 microsomal enzyme induction. The relevance of this mouse data to humans is unknown. Female rats receiving duloxetine (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, duloxetine 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.
Hypromellose acetate succinate
Sucrose
Sugar spheres
Talc
Titanium dioxide (E171)
Triethyl citrate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage

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

Manufacturer: Eli Lilly and Company
License Holder: Elil Lilly Israel Ltd.,
P.O.Box 2160, Herzliya 46120.

This leaflet format was set by MOH and its content has been reviewed and approved.

X CYMB 07