APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS **S5**

1. NAME OF THE MEDICINE

CYMBALTA 30 (hard gastro-resistant capsules)

CYMBALTA 60 (hard gastro-resistant capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cymbalta 30

Each capsule contains 30 mg duloxetine (as hydrochloride).

Each capsule may contain up to 56 mg sucrose.

Cymbalta 60

Each capsule contains 60 mg duloxetine (as hydrochloride).

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 30 (Capsule)

Opaque white body, imprinted with “30 mg” in green ink, and opaque blue cap. The capsule contains white to light greyish white enteric coated pellets**.**

CYMBALTA 60 (Capsule)

Opaque green body, imprinted with “60 mg” in white ink, and opaque blue cap. The capsule contains white to light greyish white enteric coated pellets.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

CYMBALTA is indicated for:

- The treatment of depression (as defined by DSM-IV criteria)
- The treatment of Diabetic Peripheral Neuropathic Pain (DPNP)

4.2. Posology and method of administration

Posology

Depression

CYMBALTA should be initiated and maintained at a dose of 60 mg once daily without regard to meals. Although doses up to 120 mg per day have been used the efficacy of the 120 mg dose was not statistically different from that of the 60 mg once daily dose and the adverse event rate was higher with the 120 mg dose.

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

Diabetic peripheral neuropathic pain

CYMBALTA should be administered at a dose of 60 mg once daily without regard to meals. Although doses up to 120 mg per day have been used the efficacy of the 120 mg dose was not statistically significantly different from that of the 60 mg once daily dose and the adverse event rate was higher with the 120 mg dose.

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).

Special populations

Renal impairment

Initial dose should be 30 mg once daily in patients with mild to moderate impairment of renal function (see sections 4.3, 4.4 and 5.2).

Hepatic impairment

Initial dose should be 30 mg once daily in patients with mild to moderate impairment of hepatic function (see sections 4.3, 4.4 and 5.2).

Elderly

No dosage adjustment is recommended for elderly patients 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 depression, for which data are limited (see sections 4.4 and 5.2).

Paediatric population

CYMBALTA is not indicated for use in patients under 18 years of age.

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 medical practitioners may continue decreasing the dose, but at a more gradual rate.

Method of administration

For oral use.

4.3. Contraindications

CYMBALTA is contraindicated in patients with a known hypersensitivity to the active substance, duloxetine, or to any of the excipients, listed in section 6.1.

Pregnancy and lactation (see section 4.6).

Severe impairment of hepatic function (Child-Pugh C).

Advanced renal impairment (creatinine clearance < 30 ml/min).

Concomitant use of monoamine oxidase inhibitors (MAOIs) including linezolid (see section 4.4 and 4.5).

Patients under 18 years of age.

4.4. Special warnings and precautions for use

Suicide

The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial medicine therapy. Cases of suicidal ideation and suicidal behaviours have been reported during CYMBALTA therapy or early after treatment discontinuation.

CYMBALTA is not indicated for use in patients under the age of 18.
Analyses from pooled studies of antidepressants such as CYMBALTA in psychiatric disorders found an increased risk for suicidal ideation and/or suicidal behaviours in paediatric and young adult (< 25 years of age) patients compared to placebo.

Medical practitioners should encourage patients to report any distressing thoughts or feelings at any time.

Activation of mania/hypomania

CYMBALTA should be used cautiously in patients with a history of mania or a diagnosis of bipolar disorder.

Seizures

CYMBALTA should be used cautiously in patients with a history of a seizure disorder.

Mydriasis

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

Renal or hepatic impairment

Increased plasma concentrations of CYMBALTA occur in patients with renal impairment or hepatic impairment. An initial dose of 30 mg once daily should be used in patients with renal impairment and those with mild to moderate hepatic impairment (Child-Pugh A and B) (see sections 4.2, 4.2 and 5.2).

Hepatitis/elevated liver enzymes

Elevations in liver enzymes, hepatitis and jaundice have been reported in patients treated with CYMBALTA. Severe elevations of liver enzymes (> 10 x upper limit of normal) or liver injury with a cholestatic or mixed pattern have been reported, in some cases associated with excessive alcohol use or pre-existing liver disease. CYMBALTA should be used with caution in patients with substantial alcohol use or pre-existing liver disease.

Blood pressure and heart rate

CYMBALTA is associated with an increase in blood pressure. In patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended as appropriate. CYMBALTA should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure. 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 CYMBALTA should not be initiated.

Hyponatraemia

Cases of hyponatraemia (some with serum sodium lower than 110 mmol/litre) have been reported. The majority of these cases occurred in elderly patients, especially when coupled with a recent history of altered fluid balance or conditions pre-disposing to altered fluid balance. Hyponatraemia may present with nonspecific signs and symptoms (such as dizziness, weakness, nausea, vomiting, confusion, somnolence, and lethargy). Signs and symptoms associated with more severe cases have included syncopal episodes, falls and seizure.

Haemorrhage

CYMBALTA, may increase the risk of bleeding events, such as ecchymoses, purpura and gastrointestinal bleeding (see section 4.8). CYMBALTA may increase the risk of postpartum haemorrhage (see section 4.6). Therefore, caution is advised in patients taking CYMBALTA concomitantly with anticoagulants and/or medicines known to affect platelet function (e.g. NSAIDs, aspirin) and in patients with known bleeding tendencies**.**

Serotonin syndrome

A potentially life-threatening condition may occur with CYMBALTA treatment, particularly with concomitant use of other serotonergic medicine (including SSRIs, SNRIs tricyclic antidepressants or triptans), with medicines 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 medicines 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*).

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 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 to 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 depression are limited. Therefore, caution should be exercised when treating the elderly with the maximum dosage (see sections 4.2 and 5.2).

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.

Other medicinal products containing duloxetine

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

Sexual dysfunction

CYMBALTA 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 CYMBALTA.

CYMBALTA contains 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 medicines and other forms of interaction

MAOIs (Monoamine Oxidase Inhibitors)

Due to the risk of serotonin syndrome, CYMBALTA should not be used concomitantly with a monoamine oxidase inhibitor (MAOI) including linezolid and moclobemide or within at least 14 days of discontinuing treatment with a MAOI. Based on the half-life of CYMBALTA, at least 5 days should be allowed after stopping CYMBALTA, before starting a MAOI (see section 4.3).

Inhibitors of CYP1A2

Because CYP1A2 is involved in CYMBALTA metabolism, concomitant use of CYMBALTA with inhibitors of CYP1A2 will 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 %. Caution is advised if administering CYMBALTA with inhibitors of CYP1A2 (e.g. quinolone antibiotics) and a lower CYMBALTA dose should be used.

Inhibitors of CYP2D6

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

CNS medicines

Caution is advised when CYMBALTA is taken in combination with other centrally acting medicines and substances, including alcohol and sedative medicinal products (e.g. benzodiazepines, morphinomimetics, antipsychotics, phenobarbital, sedative antihistamines).

Serotonergic medicines

Concomitant use of other medicines with serotonergic activity like SNRIs, SSRIs, tricyclic antidepressants like clomipramine or amitriptyline, MAOIs like moclobemide and linezolid, St John's wort (*Hypericum perforatum*) or triptans, tramadol, pethidine and tryptophan may result in serotonin syndrome (see section 4.4).

Medicines highly bound to plasma protein

CYMBALTA is highly bound to plasma proteins (> 90 %). Therefore, administration of CYMBALTA to a patient taking another medicine that is highly protein bound may cause an increase in free concentrations of either medicine.

Effect of CYMBALTA on other medicines

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

Medicines metabolised by CYP2D6: CYMBALTA is a moderate inhibitor of CYP2D6. When CYMBALTA was administered at the 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) increased steady-state AUC of tolterodine (2 mg twice daily) by 71 % but did not affect the pharmacokinetics of the 5-hydroxyl metabolite. Therefore, caution should be used if CYMBALTA is co-administered with medications that are predominantly metabolised by the CYP2D6 system (risperidone and tricyclic antidepressants such as nortriptyline, amitriptyline and imipramine), and which have a narrow therapeutic index (such as flecainide, propafenone and metoprolol).

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

Anticoagulants and antiplatelet medicines: Caution should be exercised when CYMBALTA is combined with oral anticoagulants or antiplatelet medicines 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 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 medicines 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 duloxetine 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

Pregnancy

Safety in pregnant women has not been established.

CYMBALTA should not be used during pregnancy. Discontinuation symptoms (e.g. hypotonia, tremor, jitteriness, feeding difficulty, respiratory distress and seizures) may occur in the neonate after maternal CYMBALTA use near term (see section 4.3).

In a study, maternal exposure to duloxetine 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 duloxetine late in pregnancy). The majority occurred between 35 and 36 weeks of gestation.

Observational data have provided evidence of an increased risk (less than 2-fold) of postpartum haemorrhage following CYMBALTA exposure within the month prior to birth.

Epidemiological data have suggested that the use of SSRIs, such as CYMBALTA, 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 SNRI 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).

Breastfeeding

The safety of CYMBALTA has not been established in women who are breastfeeding their infants. CYMBALTA is excreted into the milk of lactating women. Women who are taking CYMBALTA should not breastfeed their infants (see section 4.3).

Fertility

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

4.7. Effects on ability to drive and use machines

CYMBALTA may be associated with undesirable effects, such as sedation and dizziness. Therefore, patients should be cautioned about operating hazardous machinery, including automobiles, while taking CYMBALTA.

4.8. Undesirable effects

a. Summary of the safety profile

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.

b. Tabulated summary of adverse reactions

Table 1 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials.

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).

Very common	**Common**	**Uncommon**	**Rare**	**Very Rare**
Infections and infestations				
		Laryngitis		
Immune system disorders				
			Anaphylactic reaction; Hyper-sensitivity disorder	
Endocrine disorders				
			Hypothyroidism	
Metabolism and nutrition disorders				
	Decreased appetite	Hyperglycaemia (reported especially in diabetic patients)	Dehydration; Hyponatraemia SIADH[6]	
Psychiatric disorders				
	Insomnia;	Suicidal ideation[5,7];	Suicidal	

	Agitation; Libido decreased; Anxiety; Orgasm abnormal; Abnormal dreams	Sleep disorder; Bruxism; Disorientation; Apathy	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 leg syndrome; Poor quality sleep	Serotonin syndrome[6]; Convulsion[1]; Psychomotor restlessness[6]; Extra-pyramidal symptoms[6]	
Eye disorders				
	Vision blurred	Mydriasis;	Glaucoma	

		Visual impairment		
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; 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 disorders				
	Sweating increased; Rash	Night sweats; Urticaria; Dermatitis contact; Cold sweat; Photosensitivity reaction; Increased tendency to bruise	Stevens-Johnson Syndrome[6]; Angio-neurotic oedema[6]	Cutaneous vasculitis

Musculoskeletal and connective tissue disorders				
	Musculoskeletal 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 decreased	Weight increased; 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 duloxetine 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.

c. Description of selected adverse reactions

Discontinuation symptoms have been reported when stopping CYMBALTA. The most commonly reported symptoms following abrupt or tapered discontinuation of CYMBALTA in clinical trials have included dizziness, nausea and or vomiting, headache, paraesthesia or electric shock-like sensations particularly in the head, fatigue, vomiting, irritability, nightmares, insomnia, fatigue, somnolence, diarrhoea, agitation or anxiety, tremor, hyperhidrosis, vertigo, somnolence and myalgia.

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).

CYMBALTA treatment in placebo-controlled clinical trials was associated with mean increases from baseline to endpoint in ALT, AST and CPK and potassium. In some cases, abnormal values were observed for these analytes in CYMBALTA-treated patients compared with placebo-treated patients.

Glucose regulation: In three clinical trials of CYMBALTA for the treatment of diabetic neuropathic pain, the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 9,048 mmol/l (176 mg/dl) and the mean baseline haemoglobin A_{1c} (HbA_{1C}) was 7,81 %.

In the 12-week acute treatment phase of these studies, increases in fasting blood glucose were observed in CYMBALTA-treated patients. HbA_{1c} 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 HbA_{1C} in both the CYMBALTA and the routine care groups, but the mean increase was 0,3 % greater in the CYMBALTA treated group. There was also an increase in fasting blood glucose and in total cholesterol in CYMBALTA-treated patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications – https://www.sahpra.org.za/Publications/Index/8. Alternatively, report suspected adverse events to the company at ade_za@lilly.com.

4.9. Overdose

Signs and symptoms

Fatal outcomes have been reported for acute overdoses at doses as low as approximately 1000 mg. Signs and symptoms of overdose (CYMBALTA alone or with mixed medicines) included somnolence, coma, serotonin syndrome, seizures, vomiting and tachycardia.

Management of overdose

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

supportive measures. 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

Duloxetine is a combined serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine reuptake inhibitor (SNRI). Duloxetine weakly inhibits dopamine uptake with no significant affinity for histaminergic, dopaminergic, cholinergic or adrenergic receptors.

Duloxetine dose-dependently increased extracellular levels of serotonin and norepinephrine in various brain areas of animals.

The pain inhibitory action of duloxetine is believed to be a result of potentiation of descending inhibitory pain pathways within the CNS.

The presumed mechanism of action of duloxetine in the treatment of depression is thought to be due to its inhibition of neuronal uptake of serotonin and norepinephrine and a resultant increase in serotonergic and noradrenergic neurotransmission in the CNS.

Elderly

The effect of duloxetine 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 HAMD17

score for duloxetine-treated patients compared to placebo. Tolerability of duloxetine 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 (120 mg per day) are limited and thus, caution is recommended when treating this population.

5.2. Pharmacokinetic properties

Absorption

Duloxetine is well absorbed after oral administration, with the C_{max} occurring 6 hours post-dose. Food delays the time to reach peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11 %). Steady state plasma concentrations are achieved after 3 days of dosing.

Distribution

Duloxetine is highly bound (> 90 %) primarily to albumin and α_1-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 CYP2D6 and CYP1A2 catalyse the formation of two major metabolites (glucuronide conjugate of 4-hydroxy duloxetine and sulphate conjugate of 5-hydroxy, 6-methoxy duloxetine). Circulating metabolites are not pharmacologically active.

Elimination

The mean elimination half-life of duloxetine is 12,1 hours. The mean plasma clearance of duloxetine is 101 l/hr.

Special Populations

Gender: Pharmacokinetic differences have been identified between males and females. The mean plasma clearance was 9 % to 55 % lower in females, but the duloxetine half-life was similar between males and females. Some women may need a lower dose.

Smoking status: Duloxetine bioavailability appears to be 34 % lower in smokers than in non-smokers.

Age: Pharmacokinetic differences have been identified between middle age and elderly females (AUC is 24 % higher and half-life is 4,3 hours longer in the elderly) (see sections 4.2 and 4.4).

Renal impairment: End-stage renal disease patients receiving chronic intermittent haemodialysis had 2-fold higher duloxetine C_{max} and AUC values compared to healthy patients. Therefore, a lower dose should be used in patients with clinically significant renal impairment (see sections 4.2 and 4.3).

Hepatic impairment: The half-life of duloxetine was 34 hours longer in patients with moderate cirrhosis of the liver, Child Pugh B, and exposure as AUC was approximately increased four fold. Therefore, a lower dose should be used for patients with mild to moderate liver impairment (see sections 4.2 and 4.3).

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).

Studies in juvenile rats reveal transient effects on neurobehaviour, as well as significantly decreased body weight and food consumption; hepatic enzyme induction; and hepatocellular vacuolation at 45 mg/kg/day. The general toxicity profile of duloxetine in juvenile rats was similar to that in adult rats. The no-adverse effect level was determined to be 20 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Capsule content:

Hypromellose

Hypromellose acetate succinate

Sucrose

Sugar spheres

Talc

Titanium dioxide

Triethyl citrate

Capsule shell:

CYMBALTA 30 mg

Gelatin

Sodium lauryl sulfate

Titanium dioxide

Indigo carmine

Edible green ink

Edible green ink contains:

Black iron oxide - synthetic

Yellow iron oxide - synthetic

Propylene glycol

Shellac

CYMBALTA 60 mg

Gelatin

Sodium lauryl sulfate

Titanium dioxide

Indigo carmine

Yellow iron oxide

Edible white ink

Edible white ink contains:

Titanium dioxide

Propylene glycol Shellac

Povidone

6.2. Incompatibilities

Not applicable.

6.3. Shelf-life

24 months

6.4. Special precautions for storage

Store at or below 30 °C in blister packs.

Keep out of the reach of children.

6.5. Nature and contents of container

CYMBALTA capsules are supplied in blister packs composed of cold-form aluminium laminate on one side and vinyl coated aluminium foil on the other side and packed in cartons of 28 capsules.

6.6. Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Eli Lilly (S.A.) (Pty) Ltd

First Floor, Golden Oak House, Ballyoaks Office Park,

35 Ballyclare Drive,

Bryanston,

Johannesburg,

South Africa

8. REGISTRATION NUMBER(S)

CYMBALTA 30: 37/1.2/0299

CYMBALTA 60: 37/1.2/0301

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

CYMBALTA 30: 17 April 2009

CYMBALTA 60: 17 September 2004

10. DATE OF REVISION OF THE TEXT

24 January 2022