APPROVED PACKAGE INSERT

SCHEDULING STATUS: S5

PROPRIETARY NAMES AND DOSAGE FORM:

CYMBALTA 30 (Capsules)

CYMBALTA 60 (Capsules)

COMPOSITION:

Each delayed-release capsule for oral administration contains enteric-coated pellets of duloxetine hydrochloride equivalent to 30 mg or 60 mg of duloxetine that are designed to prevent degradation of the medicine in the acidic environment of the stomach.

PHARMACOLOGICAL CLASSIFICATION:

A 1.2 Psychoanaleptics (antidepressants)

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Duloxetine is a serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine reuptake inhibitor (SNRI) and is chemically unrelated to tricyclic and tetracyclic antidepressant agents. 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.

Neurochemical and behavioural studies in laboratory animals showed an enhancement of both serotonin and norepinephrine neurotransmission in the central nervous system (CNS).
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.

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 %) to plasma proteins; primarily to albumin and α_1-acid glycoprotein. Protein binding is not affected by renal or hepatic impairment.

Metabolism: Duloxetine is extensively metabolised and the metabolites are excreted principally in urine. Both CYP2D6 and CYP1A2 catalyze the formation of two major metabolites (glucuronide conjugate of 4-hydroxy duloxetine, sulphate conjugate of 5-hydroxy, 6-methoxy duloxetine). Circulating metabolites are not pharmacologically active.

Excretion: 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.

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).

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

Hepatic impairment*:* The half-life of duloxetine was 34 hours longer in patients with cirrhosis of the liver and clearance was approximately 15 % of that for age and gender-matched healthy subjects. Therefore, a lower dose should be used for patients with mild to moderate liver impairment. (See 'DOSAGE AND DIRECTIONS FOR USE' and 'CONTRA-INDICATIONS').

INDICATIONS:

CYMBALTA is indicated for the treatment of depression (as defined by DSM-IV criteria).

CYMBALTA is indicated for the treatment of diabetic peripheral neuropathic pain (DPNP).

CONTRA-INDICATIONS:

CYMBALTA is contra-indicated in patients with a known hypersensitivity to duloxetine or to any of the excipients.

Pregnancy and lactation.

Severe impairment of hepatic function.

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

Concomitant use of monoamine oxidase inhibitors (MAOIs). (See also 'WARNINGS')

WARNINGS:

MAOIs (Monoamine Oxidase Inhibitors): CYMBALTA should not be used 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.

INTERACTIONS:

Interaction with other medicinal products and other forms of interaction:

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.

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), an 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.

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 and which have a narrow therapeutic index.

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.

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.

PREGNANCY AND LACTATION:

Pregnancy: Safety in pregnant women has not been established. There was no evidence of teratogenicity in animal studies. (See 'CONTRA-INDICATIONS'.)

Breast feeding mothers: The safety of CYMBALTA has not been established in breastfeeding women. CYMBALTA and/or its metabolites are excreted into the milk of lactating rats. (See 'CONTRA-INDICATIONS').

DOSAGE AND DIRECTIONS FOR USE:

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 significantly different from that of the 60 mg once daily dose and the adverse event rate was higher with the 120 mg dose.

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.

Renal impairment: Initial dose should be 30 mg once daily in patients with mild to moderate impairment of renal function. (See 'Special precautions', 'Pharmacokinetic properties' and 'CONTRA-INDICATIONS'.)

Hepatic impairment: Initial dose should be lower or less frequent in patients with mild to moderate impairment of hepatic function. (See 'Special precautions', 'Pharmacokinetic properties' and 'CONTRA-INDICATIONS').

Age: No dosage adjustment is recommended for elderly patients on the basis of age. Safety and efficacy have not been established in patients under the age of 18 years.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side effects:

CLINICAL TRIAL DATA:

Adverse events observed during clinical trials for depression and diabetic peripheral neuropathic pain are as follows:

EVENT	**FREQUENCY OF OCCURRENCE** *** ≥ 10 % reported ** ≥ 1 % - < 10 % reported * ≥ 0,1 % and < 1 % reported † < 0,1 % reported		
System Organ Class / MedDRA Preferred Term	**All** **N=4 763**	**Depression** **N=1 522**	**DPNP** **N=800**
Cardiac Disorders			
Palpitations	**	**	*
Tachycardia	*	*	*
Ear and Labyrinth Disorders			
Vertigo	*	*	**
Eye Disorders			
Vision blurred	**	**	**
Mydriasis	*	*	-
Visual disturbance	*	*	*

Gastrointestinal Disorders			
Constipation	***	***	**
Dry mouth	***	***	**
Nausea	***	***	***
Diarrhoea	**	**	**
Vomiting	**	**	**
Dyspepsia	**	**	**
Eructation	*	*	†
Gastroenteritis	*	*	*
Stomatitis	*	*	†
General Disorders and Administration Site Conditions			
Fatigue[1]	***	**	**
Rigors	**	*	*
Feeling abnormal	*	*	*
Feeling hot and / or cold	*	*	*
Malaise	*	*	*
Thirst	*	*	*
Investigations			
Weight decreased	**	**	**
Blood pressure increased	*	*	†
Hepatic lab related findings	*	*	**
Weight increased	*	*	*

Metabolism and Nutrition Disorders			
Decreased appetite[2]	**	**	**
Dehydration	*	†	†
Musculoskeletal and Connective Tissue Disorders			
Muscle tightness	*	**	*
Muscle twitching	*	**	*
Nervous System Disorders			
Dizziness	***	**	***
Headache[3]	***	***	***
Lethargy	**	**	**
Somnolence[4]	**	**	***
Tremor	**	**	**
Dysgeusia	*	*	**
Psychiatric Disorders			
Insomnia[5]	***	**	**
Anorgasmia[6]	**	**	*
Libido decreased[7]	**	**	*
Anxiety	**	**	**
Sleep disorder	**	*	**
Agitation[8]	*	*	*
Bruxism	*	*	-
Disorientation	*	†	*

Renal and Urinary Disorders			
Nocturia	*	-	*
Urinary hesitation	*	*	**
Reproductive System and Breast Disorders			
Ejaculation disorder[9]	**	**	*
Erectile dysfunction	**	**	**
Respiratory, Thoracic and Mediastinal Disorders			
Yawning	**	**	*
Skin and Subcutaneous Tissue Disorders			
Hyperhidrosis	**	**	**
Night sweats	*	**	*
Photosensitivity reaction	*	†	†
Vascular Disorders			
Hot flush	**	**	**
Flushing	*	*	*
Peripheral coldness	*	*	*

[1]Also includes asthenia

[2]Previously listed under anorexia and decreased appetite, or anorexia and appetite decreased

[3]Placebo rate was less than duloxetine rate (MDD only)

[4]Also includes hypersomnia, sedation

[5]Also includes middle insomnia (refers to middle of the night insomnia)

[6]Also includes abnormal orgasm

[7]Also includes loss of libido

[8]Also includes feeling jittery, nervousness, restlessness, tension

[9]Also includes ejaculation delayed

Dizziness, nausea and headache (≥ 5 %) were also reported as common adverse events upon CYMBALTA discontinuation.

CYMBALTA treatment in placebo-controlled clinical trials was associated with increases in ALT, AST and CPK in CYMBALTA -treated patients.

Glucose regulation: In clinical trials of CYMBALTA for the treatment of diabetic neuropathic pain, the mean duration of diabetes was approximately 11 years, the mean baseline fasting blood glucose was 9,048 mmol/l and the mean baseline haemoglobin A_{1c} (HbA_{1c}) was 7,80 %. In these studies, small increases in fasting blood glucose were observed in CYMBALTA-treated patients compared to placebo at 12 weeks and routine care at 52 weeks. The increase was similar at both time points. Relative to placebo or routine care, mean HbA_{1c} values were stable, there was no mean weight gain, mean lipid concentrations (cholesterol, LDL, HDL, triglycerides) were stable and there were no differences in incidence of serious and non-serious diabetes-related adverse events.

SPONTANEOUS DATA: (For depression and DPNP)

The following list of undesirable effects (adverse drug reactions) is based on post-marketing spontaneous reports:

Eye disorders:

Glaucoma.

Hepatobiliary disorders:

Hepatitis, jaundice.

Immune system disorders:

Anaphylactic reaction.

Investigations:

AST increased, ALT increased, alkaline phosphatase increased**,** bilirubin increased.

Metabolism and nutrition disorders:

Hyponatraemia.

Skin and subcutaneous tissue disorders: Rash, angioneurotic oedema, Stevens-Johnson syndrome, urticaria.

Vascular disorders: Orthostatic hypotension (especially at the initiation of treatment), syncope (especially at initiation of treatment).

Special precautions:

Activation of mania/hypomania: CYMBALTA should be used cautiously in patients with a history of mania.

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

Mydriasis: Mydriasis has been reported in association with duloxetine; 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. A lower starting dose should be used in such patients (see 'DOSAGE AND DIRECTIONS FOR USE', 'Pharmacokinetic properties' and 'CONTRA-INDICATIONS').

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 has not been studied in patients under the age of 18 and is not intended for use in this age group. However, pooled and some individual data analyses from studies of some antidepressants in psychiatric conditions indicate a potential increased risk for suicidal ideation and suicidal behaviours in paediatric patients compared to placebo.

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

Increased blood pressure: CYMBALTA is associated with an increase in blood pressure in some patients. In patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended as appropriate.

Elevated liver enzymes: Elevations in liver enzymes were seen in some patients treated with CYMBALTA in clinical trials. These were usually transient and self-limiting, or resolved upon discontinuation of CYMBALTA. Severe elevations of liver enzymes (> 10x upper limit of normal) or liver injury with a cholestatic or mixed pattern have been rarely reported, in some cases associated with excessive alcohol use. CYMBALTA should be used with caution in patients with substantial alcohol use.

Effects on the 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

Carcinogenesis, mutagenesis and impairment of fertility:

Carcinogenesis: CYMBALTA was administered in the diet to rats and mice for 2 years. In rats, CYMBALTA did not cause any increase in incidence of expected or unusual neoplasms or decrease in the latency for any tumour type. In female mice receiving CYMBALTA, there was an increased incidence of hepatocellular adenomas and carcinomas at the high dose only (144 mg/kg/day), but these were considered to be secondary to hepatic enzyme induction with associated centrilobular hypertrophy and vacuolation. The relevance of this mouse data in humans is unknown.

Mutagenesis: CYMBALTA demonstrated no mutagenic potential in a battery of *in vitro* and *in vivo* genotoxicity tests.

Impairment of fertility: Reproductive performance was not affected in male rats receiving CYMBALTA (45 mg/kg/day). In female rats receiving CYMBALTA (45 mg/kg/day), reproductive toxicity was demonstrated by a decrease in maternal food consumption and body weight, oestrous cycle disruption, depressions in live birth indices and progeny survival and progeny growth

retardation. The no-observed-effect level (NOEL) for maternal toxicity, reproductive toxicity and developmental toxicity in the female fertility study was 10 mg/kg/day. The relevance of this preclinical data in humans is unknown.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Signs and symptoms:

There is limited clinical experience with CYMBALTA overdose in humans. In premarketing clinical trials, no cases of fatal overdose of CYMBALTA have been reported. Four non-fatal acute ingestions of CYMBALTA (300 to 1 400 mg), alone or in combination with other medicines have been reported. The predicted signs would be related to the central nervous and gastrointestinal systems (e.g. tremors, clonic convulsions, ataxia, emesis and decreased appetite).

Management of overdose:

No specific antidote is known. An airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal may be useful in limiting absorption. CYMBALTA has a large volume of distribution and forced diuresis, haemoperfusion and exchange perfusion are unlikely to be beneficial.

IDENTIFICATION:

CYMBALTA 30 (Capsule), UC9543, has an opaque white body and opaque blue cap and is imprinted with ‘30 mg’ on the body in green ink. The capsule contains white to light greyish white enteric coated pellets.

CYMBALTA 60 (Capsule), UC9542, has an opaque green body and opaque blue cap and is imprinted with '60 mg' on the body in white ink. The capsule contains white to light greyish white enteric coated pellets.

PRESENTATION:

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.

STORAGE INSTRUCTIONS:

Store below 30 ºC in blister packs.

Keep out of the reach of children.

REGISTRATION NUMBERS:

37/1.2/0299 for the 30 mg capsule

37/1.2/0301 for the 60 mg capsule

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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

1 Petunia Street

Bryanston

2021

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

20 April 2009 Lilly Logo

Registration Details for Botswana: Schedule 2	
Cymbalta 30 mg capsules Cymbalta 60 mg capsules	BOT 0700951 BOT 0700950

Registration Details for Namibia Schedule 3	
Cymbalta 30 mg capsules Cymbalta 60 mg capsules	Reg No.: 06/1.2/0006 Reg. No. 06/1.2/0007

SKEDULERINGSTATUS: S5

EIENDOMSNAME EN DOSEERVORM:

CYMBALTA 30 (Kapsules)

CYMBALTA 60 (Kapsules)

SAMESTELLING:

Elke langwerkende vrystellingkapsule vir mondelike toediening bevat enteries bedekte korrels duloksetienhidrochloried, ekwivalent aan 30 mg of 60 mg duloksetien, wat ontwerp is om degradering van die medisyne in die suur omgewing van die maag te voorkom.

FARMAKOLOGIESE KLASSIFIKASIE:

A 1.2 Psigo-analeptika (antidepressante)

FARMAKOLOGIESE WERKING:

Farmakodinamiese eienskappe:

Duloksetien is ʼn serotonien (5-hidroksitriptamien, 5-HT) en norepinefrien heropnameïnhibeerder (SNHI), en is chemies nie verwant aan trisikliese en tetrasikliese antidepressante nie. Duloksetien is ʼn swak inhibeerder van dopamienopname, met geen noemenswaardige affiniteit vir histaminergiese, dopaminergiese, cholinergiese en adrenergiese reseptore nie.

Duloksetien het op ʼn dosisafhanklike manier die ekstrasellulêre vlakke van serotonien en norepinefrien in verskeie breinareas van diere verhoog.

Neurochemiese en gedragstudies in laboratoriumdiere het ʼn verbetering van beide die serotonien- en norepinefrien neurotransmissie in die sentrale senuwee stelsel getoon.

Daar word geglo dat die pyn inhibeerende aksie van duloksetien, aan die resultaat van 'n versterkte dalende inhibisie baan binne die sentrale senuwee stelsel toegeskryf kan word.

Daar word geglo dat die vermoedelike metode van werking van duloksetien in die behandeling van depressie die gevolg van sy inhibisie van die neuronale opname van serotonien en norepinefrien is, met ʼn gevolglike toename in serotonergiese en noradrenergiese neurotransmissie in die sentrale senuwee stelsel.

Farmakokinetiese eienskappe:

Absorpsie: Duloksetien word goed na mondelike toediening geabsorbeer, met die K_{maks} 6 uur na dosering. Voedsel vertraag die bereiking van piek konsentrasies van 6 tot 10 uur en verminder die mate van absorpsie minimaal (ongeveer 11 %). Stabiele-staat plasmakonsentrasies word tipies na 3 dae van dosering bereik.

Verspreiding: Duloksetien word sterk (> 90 %) aan plasmaproteïene gebind; hoofsaaklik aan albumien en α_1-suurglukoproteïen. Proteïenbinding word nie deur belemmerde nier- of lewerfunksie beïnvloed nie.

Metabolisme: Duloksetien word uitgebreid gemetaboliseer en die metaboliete word hoofsaaklik in die urien uitgeskei. Beide CYP2D6 en CYP1A2 kataliseer die vorming van twee belangrike metaboliete (die glukuronkonjugaat van 4-hidroksiduloksetien en die sulfaatkonjugaat van 5-hidroksie, 6-metoksiduloksetien). Die sirkulerende metaboliete is nie farmakologies aktief nie.

Uitskeiding: Die gemiddelde eliminasiehalfleeftyd van duloksetien is 12,1 uur. Die gemiddelde plasmasuiwering van duloksetien is 101 L/uur.

Spesiale populasies:

Geslag: Farmakokinetiese verskille is wel tussen mans en vroue geïdentifiseer. Die oënskynlike plasmasuiwering was 9 % tot 55 % laer in vroue, maar die duloksetien half-leeftyd was soortgelyk tussen mans en vrouens.

Rokers-status: Dit wil voorkom asof duloksetien bio-beskikbaarheid tot 34 % laer in rokers as in nie-rokers is.

Ouderdom: Farmakokinetiese verskille is wel tussen middeljarige en bejaarde vroue geïdentifiseer (AOK is 24 % hoër en die halfleeftyd langer as 4,3 uur in bejaardes).

Belemmerde nierfunksie: Pasiënte met eindstadium niersiekte wat chronies afwisselende hemodialise ontvang, het dubbel duloksetien K_{maks} en AOK- waardes in vergelyking met gesonde indiwidue gehad. Vir hierdie rede, moet ʼn laer dosering gegee word aan pasiënte met klinies beduidende nierinkorting (Sien ‘KONTRA-INDIKASIES’).

Belemmerde lewerfunksie: Pasiënte met sirrose van die lewer het ʼn aansienlik langer halfleeftyd van 34 uur gehad, terwyl die suiwering ongeveer 15 % van dié van gesonde, ouderdom- en geslagsverwante indiwidue was. Daarom behoort ʼn laer dosis in pasiënte met klinies betekenisvolle belemmerde lewerfunksie oorweeg te word. (Sien ‘DOSIS EN GEBRUIKSAANWYSINGS’).

INDIKASIES:

CYMBALTA word aangedui vir die behandeling van depressie soos deur DSM-IV kriteria aangedui.

CYMBALTA word aangedui vir die behandeling van diabetiese perifere neuropatiese pyn (DPNP).

KONTRA-INDIKASIES:

CYMBALTA word teenaangedui in pasiënte met ’n bekende hipersensitiwiteit teen duloksetien of enige van die eksipiënte.

Swangerskap en laktasie.

Erge belemmerde lewerfunksie.

Gevorderde nierinkorting (kreatinien opruiming < 30 ml/min).

Tegelyke gebruik van mono-amienoksidase inhibeerders (MAOIs). (Sien ook ‘WAARSKUWINGS’)

WAARSKUWINGS:

MAOIs (Monoamienoksidaseïnhibeerders): CYMBALTA behoort nie saam met ’n MAOI, of tenminste binne 14 dae na die staking van behandeling met ’n MAOI, gebruik te word nie. Gebaseer op die halfleeftyd van CYMBALTA, behoort ten minste 5 dae na die staking van CYMBALTA te verloop voordat daar met ’n MAOI begin kan word.

INTERAKSIES:

Interaksie met ander medisinale produkte en ander vorms van interaksie:

Medisyne wat deur CYP1A2 gemetaboliseer word: In ’n kliniese studie is die farmakokinetika van teofillien, ’n CYP1A2 substraat, nie noemenswaardig deur die gelyktydige toediening van CYMBALTA (60 mg twee keer per dag) beïnvloed nie. Uit hierdie resultate blyk dit onwaarskynlik te wees dat CYMBALTA ’n klinies betekenisvolle effek op die metabolisme van CYP1A2 substrate sal hê.

Inhibeerders van CYP1A2: Aangesien CYP1A2 by die metabolisme van CYMBALTA betrokke is, sal die gelyktydige gebruik van CYMBALTA met sterk inhibeerders van CYP1A2 waarskynlik tot hoër konsentrasies van CYMBALTA lei. Fluvoksamien (100 mg een keer per dag), ’n inhibeerder van CYP1A2, het die oënskynlik plasmasuiwering van CYMBALTA met ongeveer 77 % laat afneem. Sorg moet aan die dag gelê word wanneer CYMBALTA saam met inhibeerders van CYP1A2 (bv. sommige kinoloonantibiotika) toegedien word, en derhalwe behoort ’n laer CYMBALTA dosis gebruik te word.

Medisyne wat deur CYP2D6 gemetaboliseer word: CYMBALTA is ’n matige inhibeerder van CYP2D6. Nadat CYMBALTA teen die maksimum dosis (60 mg twee keer per dag) saam met ’n enkel dosis desipramien, ’n CYP2D6 substraat toegedien is, het die AOK van desipramien drievoudig toegeneem. Die medetoediening van CYMBALTA (40 mg twee keer per dag) het die stabiele staat AOK van tolterodien (2 mg 2 keer per dag) met 71 % verhoog, maar het nie die farmakokinetika van die 5-hidroksiel metaboliet beïnvloed nie. Daarom moet sorg aan die dag gelê word wanneer CYMBALTA saam met medikasies wat hoofsaaklik deur die CYP2D6 sisteem gemetaboliseer word en wat ’n noue terapeutiese indeks het, toegedien word.

Inhibeerders van CYP2D6: Aangesien CYP2D6 by die metabolisme van CYMBALTA betrokke is, mag die gelyktydige gebruik van duloksetien saam met sterk inhibeerders van CYP2D6 lei tot hoër konsentrasies van CYMBALTA. Paroksetien (20 mg een keer per dag) het die oënskynlike plasmasuiwering van CYMBALTA met ongeveer 37 % verminder. Sorg moet aan die dag gelê word wanneer CYMBALTA saam met inhibeerders van CYP2D6 (bv. SSHI) toegedien word.

Sentrale senuwee stelsel medisyne: Versigtigheid word aanbeveel wanneer CYMBALTA in kombinasie met ander sentraal werkende medisyne en middels, insluitende alkohol, gebruik word.

Medisyne wat sterk aan plasmaproteïene gebind is: CYMBALTA word sterk aan plasmaproteïene gebind (> 90 %). Daarom mag die toediening van CYMBALTA aan ʼn pasiënt wat ʼn ander hoogs proteïengebonde middel gebruik, ʼn toename in die vry konsentrasies van enige van die middels veroorsaak.

SWANGERSKAP EN LAKTASIE:

Swangerskap: Die veiligheid in swanger vroue is nie vasgestel nie. In dierestudies was daar geen bewyse van teratogenisiteit nie. (Sien 'KONTRA-INDIKASIES')

Moeders wat borsvoed: Die veiligheid van CYMBALTA is nie in moeders wat borsvoed vasgestel nie. Duloksetien en/of sy metaboliete word in die melk van lakterende rotte vrygestel. (Sien 'KONTRA-INDIKASIES')

DOSIS EN GEBRUIKSAANWYSINGS:

Depressie: CYMBALTA behoort begin en onderhou te word teen `n dosis van 60 mg een keer per dag ongeag van maaltye. Alhoewel doserings van tot 120 mg per dag gebruik is, was die effektiwiteit van die 120 mg dosering nie statisties beduidend teenoor die 60 mg dosering een maal per dag nie, en 'n hoër voorkoms van newe effekte is met die 120 mg dosering aangemeld.

Diabetiese perifere neuropatiese pyn: CYMBALTA behoort begin en onderhou te word teen `n dosis van 60 mg een keer per dag ongeag van maaltye. Alhoewel doserings van tot 120 mg per dag gebruik is, was die effektiwiteit van die 120 mg dosering nie statisties beduidend teenoor die 60 mg dosering een maal per dag nie, en 'n hoër voorkoms van newe effekte is met die 120 mg dosering aangemeld.

Belemmerde nierfunksie: ’n Aanvanklike dosis van 30 mg een keer per dag in pasiënte met matige tot erge belemmerde nierfunksie. (Sien ‘Spesiale voorsorgmaatreëls’, ‘Farmakokinetiese Eienskappe’ en ‘KONTRA-INDIKASIES’).

Belemmerde lewerfunksie: Die aanvanklike dosis behoort laer te wees of minder dikwels toegedien te word in pasiënte met matige tot erge lewerfunksie (Sien ‘Spesiale voorsorgmaatreëls’ en ‘Farmakokinetiese Eienskappe’ asook ‘KONTRA-INDIKASIES’).

Ouderdom: Geen dosisaanpassing word in bejaardes op grond van ouderdom aanbeveel nie. Die veiligheid en doeltreffendheid van CYMBALTA is nie in pasiënte jonger as 18 jaar bestudeer nie.

NEWE-EFFEKTE EN SPESIALE VOORSORGSMAATREËLS:

Newe-effekte:

DATA VAN KLINIESE STUDIES:

Newe effekte wat voorgekom het tydens kliniese studies op depressie, sluit die volgende in:

GEVAL	**FREKWENSIE VAN VOORKOMS** *** ≥ 10 % aangemeld ** ≥ 1 % - < 10 % aangemeld * ≥ 0,1 % en < 1 % aangemeld † < 0,1 % aangemeld		
Sisteem en Orgaan Klassifikasie/ MedDRA Verlangde Terme	**Almal N=4 763**	**Depressie N=1 522**	**DPNP N=800**
Kardiale Afwykings			

Palpitasies	**	**	*
Tagikardie	*	*	*
Oor en Labirint Afwykings			
Vertigo	*	*	**
Oogafwyking			
Belemmerde sig	**	**	**
Midriase	*	*	-
Visuele afwyking	*	*	*
Gastro-intestinale Afwykings			
Hardlywigheid	***	***	**
Droë mond	***	***	**
Naarheid	***	***	***
Diarree	**	**	**
Braking	**	**	**
Dispepsie	**	**	**
Eruktasie	*	*	†
Gastroënteritis	*	*	*
Stomatitis	*	*	†
Algemene Afwykings en Toestande by die Plek van Toediening			
Moegheid[1]	***	**	**
Styfheid	**	*	*
Gevoel van abnormaliteit	*	*	*

Gevoel van warm en/of koud	*	*	*
Malaise	*	*	*
Dors	*	*	*
Ondersoeke			
Gewigsverlies	**	**	**
Verhoging in bloeddruk	*	*	†
Hepatiese laboratorium verwante bevindinge	*	*	**
Gewigsverlies	*	*	*
Metabolisme en Voedingsafwykings			
Verlaagde eetlus[2]	**	**	**
Dehidrasie	*	†	†
Spier-skelet-stelsel en Bindweefsel Afwykings			
Spierstyfheid	*	**	*
Spiertrekkings	*	**	*
Senuwee Sisteem Afwykings			
Duiseligheid	***	**	***
Hoofpyn[3]	***	***	***
Letargie	**	**	**
Slaperigheid[4]	**	**	***
Bewing	**	**	**
Smaakafwyking	*	*	**
Psigiatriese Afwykings			
Slaaploosheid[5]	***	**	**

Anorgasmie[6]	**	**	*
Afname in libido[7]	**	**	*
Angstigheid	**	**	**
Slaap afwyking	**	*	**
Agitasie[8]	*	*	*
Bruksisme	*	*	-
Disoriëntasie	*	†	*
Afwykings van Nier-en Urinêre Stelsel			
Nokturie	*	-	*
Urien huiwering	*	*	**
Afwykings van die Bors en Reproduktiewe Stelsel			
Ejakulasie afwyking[9]	**	**	*
Erektiele disfunksie	**	**	**
Respiratoriese, Torakale- en Mediastinale Afwykings			
Gaap	**	**	*
Afwykings van die Vel en Subkutane weefsel			
Hiperhidrose	**	**	**
Nagsweet	*	**	*
Fotosensitiwiteit reaksie	*	†	†
Vaskulêre Afwykings			
Warmgloede	**	**	**
Bloos	*	*	*

Perifere koudgevoel	*	*	*

[1]Sluit ook astenie in

[2]Voorheen gelys onder anoreksie en verlaagde aptyt, of anoreksie en aptyt verlaag

[3]Plasebo syfer was laer as die van Duloksetien (MDD alleen)

[4]Sluit ook hipersomnie en sedasie in

[5]Sluit ook middel insomnie in (dit verwys na slaaploosheid in die middel van die nag)

[6]Sluit ook abnormale orgasme in

[7]Sluit ook verlies van libido in

[8]Sluit ook senuweeagtigheid, rusteloosheid en spanning in

[9]Sluit ook vertraagde ejakulasie in

Duiseligheid, naarheid en hoofpyn (≥ 5 %) is ook as algemene newe-effekte met die onttrekking van CYMBALTA aangemeld.

Behandeling met CYMBALTA in plasebo-beheerde kliniese proewe is geassosieer met toenames in ALT, AST en CPK in CYMBALTA behandelde pasiënte waargeneem.

Glukose regulering: In kliniese studies van CYMBALTA in die behandeling van diabetiese neuropatiese pyn, was die gemiddelde duur van diabetes ongeveer 11 jaar, die gemiddelde basislyn vastende bloedglukose 9,048 mml/L en die gemiddelde basislyn hemoglobin A_{1c} (HbA_{1c}) 7,80 %.

Tydens hierdie studies was effense verhogings in vastende bloedglukose waargeneem in pasiënte wat CYMBALTA ontvang het in vergelyking met die plasebo groep teen 12 weke en roetine sorg teen 52 weke. Die verhoging was dieselfde vir elke tydpunt. Relatief tot plasebo of roetine sorg, was die HbA_{1c} waardes en gemiddelde lipied konsentrasies (cholesterol, LDL, HDL en triglisseriede) stabiel,

met geen gewigstoename en geen verskil in die voorkoms van ernstige en minder ernstige diabetes verwante newe effekte nie.

SPONTANE DATA: (vir depressie en DPNP)

Die volgende lys van newe-effekte (teenstellende middel interaksies) is gebaseer op post-bemarking, spontane gevalle en die ooreenstemmende getalle wat aangemeld is:

Oogafwykings:

Gloukoom.

Hepato-bilière afwykings

Hepatitis geelsug.

Immuunsisteem afwykings:

Anafilaktiese reaksie.

Ondersoeke:

Verhoogde AST , verhoogde ALT, verhoogde alkaliese fosfatase verhoogde bilirubien.

Metabolisme- en voedingsafwykings:

Hiponatremie.

Vel en subkutane weefsel afwykings:

Uitslag, angioneurotiese edeem, Steven-Johnson sindroom en urtikaria.

Vaskulêre Afwykings:

Ortostatiese hipotensie (veral tydens die instelling van behandeling), sinkopee (veral tydens die instelling van behandeling)

Spesiale voorsorgsmaatreëls:

Aktivering van manie/hipomanie: CYMBALTA moet met sorg in pasiënte met ʼn geskiedenis van manie gebruik word.

Stuiptrekkings: CYMBALTA moet met sorg gebruik word in pasiënte met ʼn geskiedenis van `n stuiptrekkingsafwyking.

Midriase: Midriase is in assosiasie met duloksetien aangemeld; daarom moet sorg aan die dag gelê word wanneer CYMBALTA in pasiënte met verhoogde intra-okulêre druk of diegene met ʼn risiko van akute nouehoek gloukoom voorgeskryf word.

Belemmerde lewer- of nierfunksie: ʼn Toename in die plasmakonsentrasie van CYMBALTA kom voor in pasiënte met belemmerde nier- en lewerfunksie(s). ʼn Laer begindosis behoort in sulke pasiënte gebruik te word (Sien 'DOSIS EN GEBRUIKSAANWYSINGS', 'Farmakokinetiese eienskappe' en 'KONTRA-INDIKASIES').

Selfmoord: Die moontlikheid van ʼn poging tot selfmoord is inherent tot depressie en mag voortduur totdat `n noemenswaardige remissie plaasvind. Noukeurige toesig van hoë-risiko pasiënte behoort met die aanvanklike terapie gepaard te gaan. Gevalle van selfmoord idieëring en selfmoord gedrag is geraporteer gedurende behandeling met CYMBALTA, of kort na die staking daarvan.

CYMBALTA behandeling in pasiënte jonger as 18 jaar is nog nie nagevors nie, en is nie bedoel vir hierdie ouderdomsgroep nie. Nietemin, gegroepeerde en individuele data analise van studies op sekere anti-depressant terapie in psigiatriese opset het voorgestel dat daar potensieël ’n verhoogde risiko mag bestaan vir selfmoord idieëring en selfmoord optrede in pediatriese pasiënte wanneer vergelyk word met die plasebo groep.

Dokters moet pasiënte aanmoedig om enige onrusbarende gedagtes en gevoelens aan te meld.

Verhoogde bloeddruk: CYMBALTA is geassosieer met verhoging in bloeddruk in sommige pasiënte. In pasiënte met bekende hipertensie en/of ander kardiale siekte word bloeddruk monitering aanbeveel.

Verhoogde lewerensieme: Tydens kliniese studies, is verhoging van lewerensieme aangemeld in sommige pasiënte op CYMBALTA behandeling. Hierdie gevalle was meestal van verbygaande aard en selfbeperkend, of reggestel met die staking van die CYMBALTA terapie. Erge verhoging van lewerensieme (> 10x die boonste limiet van normaal) of lewerbeskadiging met cholestatiese of gemengde patroon is selde aangemeld, en in sekere gevalle geassosieer met oormatige alkohol gebruik. CYMBALTA moet met versigtigheid gebruik word in pasiënte met aansienlike alkohol gebruik.

Effek op die vermoë om te bestuur of met masjinerie te werk: CYMBALTA mag geassosieer word met ongewensde effekte soos sedasie en duiseligheid. Pasiënte moet gewaarsku word ten opsigte van die gebruik van masjinerie en motor bestuur wanneer hulle CYMBALTA gebruik.

Karsinogenese, mutagenese en belemmering van vrugbaarheid:

Karsinogenese: CYMBALTA is vir 2 jaar lank in die dieet van rotte en muise toegedien. In rotte het CYMBALTA geen toename in die insidens van verwagte of ongewone neoplasmas of `n afname in

die latensie vir enige tipe tumor veroorsaak nie. In vroulike muise wat CYMBALTA ontvang het, was daar slegs met die hoë dosis (144 mg/kg/dag) `n toename in die insidensie van hepatosellulêre adenome en karsinome. Laasgenoemde is as sekondêr beskou tot lewerensieminduksie met die geassosieerde sentrilobulêre hipertrofie en vakuolisering. Die toepaslikheid van muis data in mense is onbekend.

Mutagenese: In `n reeks *in vitro* en *in vivo* genotoksisiteit studies het CYMBALTA geen mutageniese potensiaal getoon nie.

Belemmering van vrugbaarheid: Reproduksievermoë is nie in manlike rotte wat CYMBALTA (45 mg/kg/dag) ontvang het geaffekteer nie. In vroulike rotte wat CYMBALTA (45 mg/kg/dag) ontvang het, is reproduksietoksisiteit aangetoon deur `n afname in die moeder se voerinname en liggaamsmassa, ontwrigting van die estrussiklus, onderdrukking van lewendige geboorte-indekse, oorlewing van die nageslag en belemmerde groei in die nageslag. Die geen-waargenome-effekvlak (GWEV) vir moederlike toksisiteit, reproduksietoksisiteit en ontwikkelingstoksisiteit in die vroulike vrugbaarheidstudie was 10 mg/kg/dag. Die toepaslikheid van die kliniese data in mense is onbekend.

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VAN DIE BEHANDELING DAARVAN:

Tekens en simptome:

Daar is beperkte kliniese ondervinding met oordosering met CYMBALTA in mense. In voorbemarking kliniese studies is geen gevalle van noodlottige oordosering met CYMBALTA aangemeld nie. Vier nie-noodlottige akute ingesties van CYMBALTA (300 tot 1400 mg), alleen of in kombinasie met ander medisyne, is aangemeld. Die voorspelbare tekens sal verband hou met die sentrale senuwee- en gastroïntestinale sisteme (bv. bewerasie, kloniese konvulsies, ataksie, naarheid, braking en `n afname in eetlus).

Bestuur van oordosering:

Geen spesifieke teenmiddel is bekend nie. ’n Oop-lugweg moet verseker word. Monitering van hart- en lewenstekens word aanbeveel, saam met die toepaslike simptomatiese en ondersteunende maatreëls: Maagspoeling mag aangedui wees indien dit kort na ingestie of in simptomatiese pasiënte gedoen kan word. Geaktiveerde houtskool mag nuttig in die beperking van absorpsie wees. CYMBALTA het `n groot verspreidingsvolume en geforseerde diurese, hemoperfusie en uitruilperfusie sal waarskynlik van geen nut wees nie.

IDENTIFIKASIE:

CYMBALTA 30 (Kapsule), UC9543, het ’n ondeursigtige wit liggaam en ondeursigtige blou doppie, met ‘30 mg’ in groen ink op die liggaam gedruk. Die kapsule bevat wit tot lig, gryswit, enteries bedekte korreltjies.

CYMBALTA 60 (Kapsule), UC9542, het ’n ondeursigtige groen liggaam en ondeursigtige blou doppie, met ‘60 mg’ in wit ink op die liggaam gedruk. Die kapsule bevat wit tot lig, gryswit, enteries bedekte korreltjies.

AANBIEDING:

CYMBALTA kapsules word verskaf in stulpverpakkings met aluminium laminaat, gevorm tydens ’n koue proses aan een kant, en viniel bedekte aluminium foelie aan die ander kant, verpak in kartondosies met 28 kapsules.

BERGINGSINSTRUKSIES:

Bewaar benede 30 °C in stulpverpakkings.

Hou buite bereik van kinders.

REGISTRASIENOMMERS:

37/1.2/0299 vir die 30 mg kapsule.

37/1.2/0301 vir die 60 mg kapsule.

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Eli Lilly (S.A.) (Edms) Beperk

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