CYMBALTA® (DULOXETINE) ABBREVIATED PRESCRIBING INFORMATION Presentation Hard gastro-resistant capsules, 30mg or 60mg of duloxetine. Also contains sucrose. **Uses** Treatment of major depressive disorder. Treatment of generalised anxiety disorder. Treatment of diabetic peripheral neuropathic pain (DPNP) in adults. **Dosage and Administration** *Major Depressive Disorder* Starting and maintenance dose is 60mg once daily, with or without food. Dosages up to a maximum dose of 120mg 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. After establishing response, it is recommended to continue treatment for several months, in order to avoid relapse. In patients responding to duloxetine, and with a history of repeated episodes of major depression, further long-term treatment at 60 to 120mg/day could be considered. *Generalised Anxiety Disorder* The recommended starting dose in patients with generalised anxiety disorder is 30mg once daily, with or without food. In patients with insufficient response the dose should be increased to 60mg, which is the usual maintenance dose in most patients. In patients with co-morbid major depressive disorder, the starting and maintenance dose is 60mg once daily. Doses up to 120mg per day have been shown to be efficacious and have been evaluated from a safety perspective in clinical trials. In patients with insufficient response to 60mg, escalation up to 90mg or 120mg may therefore be considered. After consolidation of the response, it is recommended to continue treatment for several months, in order to avoid relapse. *Diabetic Peripheral Neuropathic Pain* Starting and maintenance dose is 60mg daily, with or without food. Doses above 60mg/day, up to a maximum dose of 120mg/day in evenly divided doses, have been evaluated from a safety perspective. Some patients that respond insufficiently to 60mg may benefit from a higher dose. The medicinal response should be evaluated after 2 months treatment. Additional response after this time is unlikely. The therapeutic benefit should regularly be reassessed. Abrupt discontinuation should be avoided. When stopping treatment with Cymbalta the dose should be gradually reduced over at least one to two weeks to reduce the risk of withdrawal reactions. 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, continue decreasing the dose, but at a more gradual rate. **Contra-indications** Hypersensitivity to any of the components. Combination with MAOIs. Liver disease resulting in hepatic impairment. Use with potent inhibitors of CYP1A2, eg, fluvoxamine, ciprofloxacin, enoxacin. Severe renal impairment (creatinine clearance <30ml/min). Should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus. Breast-feeding is not recommended. Initiation in patients with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis. **Precautions** Do not use in children and adolescents under the age of 18. No dosage adjustment is recommended for elderly patients solely on the basis of age. However, as with any medicine, caution should be exercised. Data on the use of Cymbalta in elderly patients with generalised anxiety disorder are limited. Use with caution in patients with a history of mania, bipolar disorder, or seizures. As with other serotonergic agents, serotonin syndrome, a potentially life-threatening condition, may occur with duloxetine treatment, particularly with concomitant use of other serotonergic agents, as described under 'Interactions' (below). Caution in patients with increased intra-ocular pressure or those at risk of acute narrow-angle glaucoma. Duloxetine has been associated with an increase in blood pressure and clinically significant hypertension in some patients. In patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended as appropriate, especially during the first month of treatment. Use with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure. For patients who experience a sustained increase in blood pressure while receiving duloxetine, consider either dose reduction or gradual discontinuation. Caution in patients taking anticoagulants or products known to affect platelet function, and those with bleeding tendencies. Hyponatraemia has been reported rarely, predominantly in the elderly. 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). Adverse reactions may be more common during concomitant use of Cymbalta and herbal preparations containing St John's Wort. Monitor for suicidal thoughts, especially during first weeks of therapy, dose changes, and in patients under 25 years old. Since treatment may be associated with sedation and dizziness, patients should be cautioned about their ability to drive a car or operate hazardous machinery. Cases of akathisia/psychomotor restlessness have been reported for duloxetine. Duloxetine is used under different trademarks in several indications (major depressive disorder, generalised anxiety disorder, stress urinary incontinence, and diabetic neuropathic pain). The use of more than one of these products concomitantly should be avoided. Cases of liver injury, including severe elevations of liver enzymes (>10-times upper limit of normal), hepatitis, and jaundice have been reported with duloxetine. Most of them occurred during the first months of treatment. Duloxetine should be used with caution in patients with substantial alcohol use or with other drugs associated with hepatic injury. Capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption, or sucrose-isomaltase insufficiency should not take this medicine. **Interactions** Caution is advised when taken in combination with other centrally acting medicinal products or substances, including alcohol and sedative medicinal products; exercise caution when using in combination with antidepressants. In rare cases, serotonin syndrome has been reported in patients using SSRIs/SNRIs concomitantly with serotonergic agents. Caution is advisable if duloxetine is used concomitantly with serotonergic agents like SSRIs/SNRIs, tricyclics, MAOIs like moclobemide and linezolid, St John's Wort, antipsychotics, triptans, tramadol, pethidine, and tryptophan. Undesirable effects may be more common during use with herbal preparations containing St John's Wort. *Effects on other drugs:* Caution is advised if co-administered with 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). **Undesirable Effects** The majority of common adverse reactions were mild to moderate, usually starting early in therapy, and most tended to subside as therapy continued. Those observed from spontaneous reporting and in placebo-controlled clinical trials in depression, generalised anxiety disorder, and diabetic neuropathic pain at a rate of ≥1/100, or where the event is clinically relevant, are: *Very common (≥1/10):* Headache, somnolence, nausea, dry mouth. *Common (≥1/100 and <1/10):* Weight decrease, palpitations, dizziness, lethargy, tremor, paraesthesia, blurred vision, tinnitus, yawning, constipation, diarrhoea, abdominal pain, vomiting, dyspepsia, flatulence, sweating increased, rash, musculoskeletal pain, muscle spasm, dysuria, urinary frequency, ejaculation disorder, ejaculation delayed, decreased appetite, blood pressure increased, flushing, falls, fatigue, erectile dysfunction, insomnia, agitation, libido decreased, anxiety, orgasm abnormal, abnormal dreams. Clinical trial and spontaneous reports of anaphylactic reaction, hyperglycaemia (reported especially in diabetic patients), mania, hyponatraemia, SIADH, hallucinations, dyskinesia, serotonin syndrome, extra-pyramidal symptoms, convulsions, akathisia, psychomotor restlessness, glaucoma, mydriasis, syncope, tachycardia, supra-ventricular arrhythmia (mainly atrial fibrillation), hypertension, hypertensive crisis, epistaxis, gastritis, haematochezia, gastro-intestinal haemorrhage, hepatic failure, hepatitis, acute liver injury, angioneurotic oedema, Stevens-Johnson syndrome, trismus, and gynaecological haemorrhage have been made. Cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation. Cases of aggression and anger have been reported, particularly early in treatment or after treatment discontinuation. Cases of convulsion and tinnitus have been reported after treatment discontinuation. Discontinuation of duloxetine (particularly 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. 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. In clinical trials in patients with DPNP, small but statistically significant increases in fasting blood glucose were observed in duloxetine-treated patients compared to placebo at 12 weeks. At 52 weeks there was a small increase in fasting blood glucose and in total cholesterol in duloxetine-treated patients compared with a slight decrease in the routine care group. There was also an increase in HbA_{1c} in both groups, but the mean increase was 0.3% greater in the duloxetine-treated group. *For full details of these and other side-effects, please see the Summary of Product Characteristics, which is available at http://www.medicines.org.uk/emc/.* **Overdose** Cases of overdoses, alone or in combination with other drugs, with duloxetine doses of 5400mg have been reported. Some fatalities have occurred, primarily with mixed overdoses, but also with duloxetine alone at a dose of approximately 1000mg. Signs and symptoms of overdose (duloxetine alone or in combination with other medicinal products) included somnolence, coma, serotonin syndrome, seizures, vomiting, and tachycardia. **Legal Category** POM **Marketing Authorisation Numbers** EU/1/04/296/001, EU/1/04/296/002 **Basic NHS Cost** £22.40 per pack of 28 X 30mg capsules. £27.72 per pack of 28 X 60mg capsules. **Date of Preparation or Last Review** July 2013 **Full Prescribing Information is Available From** Eli Lilly and Company Limited, Lilly House, Priestley Road, Basingstoke, Hampshire, RG24 9NL Telephone: Basingstoke (01256) 315 000 E-mail: ukmedinfo@lilly.com Website: www.lillypro.co.uk CYMBALTA® (duloxetine) is a registered trademark of Eli Lilly and Company.

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Adverse events should be reported. Reporting forms and further information can be found at: www.mhra.gov.uk/yellowcard.

Adverse events and product complaints should also be reported to Lilly: please call Lilly UK on 01256 315 000.