Duloxa®

Duloxetine Hydrochloride

FORMS AND PRESENTATION
Duloxa® 30: Delayed Release Capsules: Box of 30.
Duloxa® 60: Delayed Release Capsules: Box of 30.

COMPOSITION
Duloxa® 30: Each delayed release capsule contains: Duloxetine hydrochloride eq. to Duloxetine 30 mg.
Duloxa® 60: Each delayed release capsule contains: Duloxetine hydrochloride eq. to Duloxetine 60 mg.
Excipients: sugar, hydroxypropyl methylcellulose, crospovidone, talc, sucrose, carboxymethyl ethylcellulose, povidone, titanium dioxide, polyethylene glycol, polysorbate, gelatin, indigotine - FD&C Blue2, yellow iron oxide (Duloxa® 60).

PHARMACOLOGICAL PROPERTIES

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.
Pharmacodynamic effects
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.

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 C_{max} 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 alpha1-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 sulfate 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.
Renal impairment: End stage renal disease (ESRD) patients receiving dialysis had 2-fold higher duloxetine C_{max} 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 7µg/day while on 40 mg twice-daily dosing. Lactation did not influence duloxetine pharmacokinetics.
Pediatric population: Pharmacokinetics of duloxetine in pediatric patients aged 7 to 17 years with major depressive disorder following oral administration of 20 to 120 mg once daily dosing regimen was characterized using population modelling analyses based on data from 3 studies. The model-predicted duloxetine steady-state plasma concentrations in pediatric patients were mostly within the concentration range observed in adult patients.

INDICATIONS
Treatment of major depressive disorder.
Treatment of diabetic peripheral neuropathic pain.
Treatment of generalised anxiety disorder.

CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients.
Concomitant use of Duloxa® with non-selective, irreversible monoamine oxidase inhibitors (MAOIs) is contraindicated.
Liver disease resulting in hepatic impairment.
Duloxa® should not be used in combination with fluvoxamine, ciprofloxacin or enoxacin (i.e., potent CYP1A2 inhibitors), since the combination results in elevated plasma concentrations of duloxetine .
Severe renal impairment (creatinine clearance <30 ml/min).
The initiation of treatment with Duloxa® is contraindicated in patients with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis.

PRECAUTIONS
Mania and Seizures
Duloxa® 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 Duloxa® 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. For patients who experience a sustained increase in blood pressure while receiving duloxetine, either dose reduction or gradual discontinuation should be considered. In patients with uncontrolled hypertension, duloxetine should not be initiated.
Renal Impairment
Increased plasma concentrations of duloxetine occur in patients with severe renal impairment on haemodialysis (creatinine clearance <30 ml/min).
Serotonin syndrome
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 (including SSRIs, SNRIs, tricyclic antidepressants or triptans), with agents that impair metabolism of serotonin such as MAOIs, or with antipsychotics or other dopamine antagonists that may affect the serotonergic neurotransmitter systems.
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 duloxetine and other serotonergic agents that may affect the serotonergic and/or dopaminergic neurotransmitter systems is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.
St John's Wort
Adverse reactions may be more common during concomitant use of Duloxa® and herbal preparations containing St John's Wort.
Suicide
Major Depressive Disorder and Generalised Anxiety Disorder: Depression is associated with an increased risk of suicidal thoughts, self-harm, and suicide.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 Duloxa® is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.
Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal thoughts prior to commencement of treatment, are known to be at greater risk of suicidal thoughts or suicidal behavior, 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 behavior with antidepressants compared to placebo in patients less than 25 years old.
Cases of suicidal thoughts and suicidal behaviors have been reported during duloxetine therapy or early after treatment discontinuation.
Close supervision of patients, and in particular those at high risk, should accompany medicinal product therapy, especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behavior or thoughts, and unusual changes in behavior, and to seek medical advice immediately if these symptoms present.
Diabetic Peripheral Neuropathic Pain
As with other medicinal products with similar pharmacological action (antidepressants), isolated cases of suicidal ideation and suicidal behaviors have been reported during duloxetine therapy or early after treatment discontinuation. Concerning risk factors for suicidality in depression, see above. Physicians should encourage patients to report any distressing thoughts or feelings at any time.
Use in Children and Adolescents Under 18 Years of Age
Duloxa® should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviors and hostility (predominantly aggression, oppositional behavior, 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 behavioral development are lacking.
Hemorrhage
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), including duloxetine. Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function (e.g., NSAIDs or acetylsalicylic acid (ASA)), and in patients with known bleeding tendencies.
Hyponatremia
Hyponatraemia has been reported when administering Duloxa®, including cases with serum sodium lower than 110 mmol/l. Hyponatraemia may be due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH). The majority of cases of hyponatraemia were reported in the elderly, especially when coupled with a recent history of, or condition pre-disposing to, altered fluid balance. Caution is required in patients at increased risk for hyponatraemia, such as elderly, cirrhotic, or dehydrated patients, or patients treated with diuretics.
Discontinuation of Treatment
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt. In clinical trials, adverse events seen on abrupt treatment discontinuation occurred in approximately 45% of patients treated with Duloxa® and 23% of patients taking placebo.
The risk of withdrawal symptoms seen with SSRIs and SNRIs may be dependent on several factors, including the duration and dose of therapy and the rate of dose reduction.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.
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 disorder, generalised anxiety disorder and stress urinary incontinence). The use of more than one of these products concomitantly should be avoided.
Hepatitis/Increased Liver Enzymes
Cases of liver injury, including severe elevations of liver enzymes (>10-times upper limit of normal), hepatitis, and jaundice have been reported with duloxetine. 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.
Ability to drive and use machines
Duloxa® 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.

PREGNANCY AND LACTATION
There are no adequate data on the use of duloxetine in pregnant women. Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). Although no studies have investigated the association of PPHN to SNRI treatment, this potential risk cannot be ruled out with duloxetine, taking into account the related mechanism of action.
As with other serotonergic medicinal products, discontinuation symptoms may occur in the neonate after maternal duloxetine use near term. Discontinuation symptoms seen with duloxetine may include hypotonia, tremor, jitteriness, feeding difficulty, respiratory distress and seizures. The majority of cases have occurred either at birth or within a few days of birth.
Duloxa® 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. As the safety of duloxetine in infants is not known, the use of Duloxa® while breast-feeding is not recommended.

DRUG INTERACTIONS
Monoamine Oxidase Inhibitors (MAOIs)
Due to the risk of serotonin syndrome, duloxetine should not be used in combination with

non-selective, 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 Duloxa® before starting an MAOI.
The concomitant use of Duloxa® with selective, reversible MAOIs, like moclobemide, is not recommended. The antibiotic linezolid is a reversible non-selective MAOI and should not be given to patients treated with Duloxa®.
Inhibitors of CYP1A2
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_{0-t} 6-fold. Therefore, Duloxa® should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine.
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 Duloxa® is taken in combination with other centrally-acting medicinal products or substances, including alcohol and sedative medicinal products (e.g., benzodiazepines, morphinomimetics, antipsychotics, phenobarbital, sedative antihistamines).
Serotonergic agents: In rare cases, serotonin syndrome has been reported in patients using SSRIs/SNRIs concomitantly with serotonergic agents. Caution is advisable if Duloxa® is used concomitantly with serotonergic agents like SSRIs, SNRIs, tricyclic antidepressants like clomipramine or amitriptyline, MAOIs like moclobemide or linezolid, St John's Wort *(Hypericum perforatum)* or triptans, tramadol, pethidine, and tryptophan.
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. Caution is advised if Duloxa® 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 H_2 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.
Inducers of CYP1A2: Population pharmacokinetic analyses have shown that smokers have almost 50% lower plasma concentrations of duloxetine compared with non-smokers.

ADVERSE EFFECTS
Adverse reactions are ranked under headings of frequency, using the following convention: Very common (≥ 1/10); Common (≥ 1/100, < 1/10); Uncommon (≥ 1/1,000, <1/100); Rare (≥ 1/10,000, < 1/1,000); Very rare (< 1/10,000), Not known (frequency cannot be estimated from available data).
- Infections and infestations: laryngitis (uncommon)
- Immune system disorders: anaphylactic reaction, hyper-sensitivity disorder (rare)
- Endocrine disorders: hypo-thyroidism (rare)
- Metabolism and nutrition disorders: decreased appetite (common); hyperglycemia in diabetic patients (uncommon); dehydration, hyponatremia, SIADH (rare)
- Psychiatric disorders: insomnia, agitation, decreased libido, anxiety, abnormal orgasm, abnormal dreams (common); suicidal ideation, sleep disorder, bruxism, disorientation, apathy (uncommon); suicidal behavior, mania, hallucinations, aggression and anger (rare)
- Nervous system disorders: headache, somnolence (very common); dizziness, lethargy, tremor, paresthesia (common); myoclonus, akathisia, nervousness, disturbance in attention, dysgeusia, dyskinesia, restless leg syndrome, poor quality sleep (uncommon); serotonin syndrome, convulsions, psychomotor restlessness, extra-pyramidal symptoms (rare)
- Eye disorders: blurred vision (common); mydriasis, visual impairment (uncommon); glaucoma (rare)
- Ear and labyrinth disorders: tinnitus (common); vertigo, ear pain (uncommon)
- Cardiac disorders: palpitations (common); tachycardia, supra-ventricular arrhythmia, mainly atrial fibrillation (uncommon)
- Vascular disorders: increased blood pressure, flushing (common); syncope, hypertension, orthostatic hypotension, peripheral coldness (uncommon) hypertensive crisis (rare)
- Respiratory, thoracic and mediastinal disorders: yawning (common); throat tightness, epistaxis (uncommon)
- Gastrointestinal disorders: nausea, dry mouth (very common); constipation, diarrhea, abdominal pain, vomiting, dyspepsia, flatulence (common); gastrointestinal hemorrhage, gastroenteritis, eructation, gastritis (uncommon); stomatitis, hematochezia, breath odor (rare)
- Hepato-biliary disorders: hepatitis, elevated liver enzymes, acute liver injury (uncommon), hepatic failure, jaundice (rare)
- Skin and subcutaneous tissue disorders: increased sweating, rash (common); night sweats, urticaria, dermatitis contact, cold sweat, photo-sensitivity reactions, increased tendency to bruise (uncommon); Stevens-Johnson Syndrome, angio-neurotic edema (rare)
- Musculoskeletal and connective tissue disorders: musculo-skeletal pain, muscle spasm (common); muscle tightness, muscle twitching (uncommon); trismus (rare)
- Renal and urinary disorders: dysuria (common); urinary retention, urinary hesitation, nocturia, polyuria, urine flow decreased (uncommon); urine odor abnormal (rare)
- Reproductive system and breast disorders: erectile dysfunction, ejaculation disorder, ejaculation delayed (common); gynecological hemorrhage, menstrual disorder, sexual dysfunction (uncommon); menopausal symptoms, galactorrhea, hyperprolactinemia (rare)
- General disorders and administration site conditions: fatigue (common); chest pain, falls, feeling abnormal, feeling cold, thirst, chills, malaise, feeling hot, gait disturbance (uncommon)
- Investigations: weight decrease (common); weight increase, increased blood creatine phosphokinase, increased blood potassium (uncommon); increased blood cholesterol (rare)

Discontinuation of Duloxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paresthesia), sleep disturbances (including insomnia and intense dreams), fatigue, somnolence, agitation or anxiety, nausea and/or vomiting, tremor, headache, irritability, diarrhea, 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.

DOSAGE AND ADMINISTRATION
Major Depressive Disorder: 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. In patients responding to duloxetine, and with a history of repeated episodes of major depression, further long-term treatment at a dose of 60 to 120 mg/day could be considered.
Generalized Anxiety Disorder: The recommended starting dose in patients with generalized anxiety disorder is 30 mg once daily with or without food. In patients with insufficient response, the dose should be increased to 60 mg, which is the usual maintenance dose in most patients.
In patients with co-morbid major depressive disorder, the starting and maintenance dose is 60 mg once daily.
Doses up to 120 mg 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 60 mg, escalation up to 90 mg or 120 mg may therefore be considered. Dose escalation should be based upon clinical response and tolerability.
After consolidation of the 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. Hence, some patients that respond insufficiently to 60 mg may benefit from a higher 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).
Special populations
Elderly
No dosage adjustment is recommended for elderly patients solely on the basis of age. However, as with any medicine, caution should be exercised when treating the elderly.
Hepatic Impairment
Duloxa® must not be used in patients with liver disease resulting in hepatic impairment.
Renal Impairment Duloxa®
No dosage adjustment is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 ml/min). Duloxa® must not be used in patients with severe renal impairment (creatinine clearance <30 ml/min).
Pediatric population
Duloxetine should not be used in children and adolescents under the age of 18 years for the treatment of major depressive disorder because of safety and efficacy concerns.
The safety and efficacy of duloxetine for the treatment of generalised anxiety disorder in paediatric patients aged 7-17 years have not been established.
The safety and efficacy of duloxetine for the treatment of diabetic peripheral neuropathic pain has not been studied. No data are available.
Discontinuation of Treatment
Abrupt discontinuation should be avoided. When stopping treatment with Duloxa® 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. 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.
Method of administration
For oral use.

OVERDOSAGE
Cases of overdoses, alone or in combination with other medicinal products, with duloxetine doses of 5400 mg 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.

STORAGE CONDITIONS
Store below 25°C.
Keep in original pack in intact conditions.

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Manufactured by:
Benta S.A.L. - Lebanon
BPI

Trademark Owner:
Abbott Healthcare Products B.V. Netherlands
Abbott

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists