For the use of Registered Medical Practitioner (Psychiatrists only)

1. GENERIC NAME & BRAND NAME

Duloxetine Delayed Release Capsule USP 20 mg
Delok® 20

Duloxetine Delayed Release Capsule USP 30 mg
Delok® 30

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Delok® 20
Each hard gelatin capsule contains:
Duloxetine Hydrochloride I.P.
Equivalent to Duloxetine…..20 mg
(As Enteric coated pallets)
Excipients……. q.s.
Colours: Ferric oxide USP-NF Red & Titanium Dioxide I.P.
Approved Colours used in Capsule shell: Sunset Yellow FCF, Titanium Dioxide I.P., Carmoisine, Ponceau 4R, Brilliant blue FCF.

Delok® 30
Each hard gelatin capsule contains:
Duloxetine Hydrochloride I.P.
Equivalent to Duloxetine…..30 mg
(As Enteric coated pallets)
Excipients……. q.s.
Colours: Ferric oxide USP-NF Red & Titanium Dioxide I.P.
Approved Colours used in Capsule shell: Titanium Dioxide I.P., Carmoisine, Sunset Yellow FCF, Erythrosine.

3. DOSAGE FORM & STRENGTH

Refer section 1 & 2

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Duloxetine was indicated by psychiatrists:

i) for the treatment of major depressive disorders in adults only.
ii) for the treatment of moderate to severe stress urinary incontinence in women.
iii) for the management of neuropathic pain associated with diabetic peripheral neuropathy.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Major depressive disorder
The recommended starting dosage in adults with MDD is 40 mg/day (given as 20 mg twice daily) to 60 mg/day (given either once daily or as 30 mg twice daily). For some patients, it may be desirable to start at 30 mg once daily for 1 week, to allow patients to adjust to duloxetine before increasing to 60 mg once daily. While a 120 mg/day dose was shown to be effective, there is no evidence that doses greater than 60 mg/day confer any additional benefits. Periodically reassess to determine the need for maintenance treatment and the appropriate dosage for such treatment.
Generalised anxiety disorder
The recommended starting dose in patients with generalised 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
Hepatic impairment
Duloxetine must not be used in patients with liver disease resulting in hepatic impairment.
Renal impairment
No dosage adjustment is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 ml/min). Duloxetine must not be used in patients with severe renal impairment (creatinine clearance <30 ml/min).
Paediatric 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.
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, especially with

duloxetine capsules 120 mg per day for major depressive disorder or generalized anxiety disorder, for which data are limited.

Discontinuation of treatment

Abrupt discontinuation should be avoided. When stopping treatment with duloxetine 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. Do not crush or chew. Swallow whole.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

Liver disease resulting in hepatic impairment.

Concomitant use of duloxetine with nonselective, irreversible monoamine oxidase inhibitors (MAOIs) is contraindicated.

Duloxetine should not be used in combination with nonselective, irreversible monoamine oxidase inhibitors - MAOIs.

Duloxetine should not be used in combination with CYP1A2 inhibitors, like fluvoxamine, ciprofloxacin or enoxacin since the combination results in elevated plasma concentrations of duloxetine.

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

The initiation of treatment with Duloxetine is contraindicated in patients with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Mania and seizures

Duloxetine should be used with caution in patients with a history of mania or a diagnosis of bipolar disorder, and/or seizures.

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 in 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 duloxetine and herbal preparations containing St John's wort (Hypericum perforatum).

Mydriasis
Mydriasis has been reported in association with duloxetine; therefore, caution should be used when prescribing duloxetine in patients with increased intraocular pressure, or those at risk of acute narrow-angle glaucoma.
Blood pressure and heart rate
Duloxetine has been associated with an increase in blood pressure and clinically significant hypertension in some patients. This may be due to the noradrenergic effect of duloxetine. Cases of hypertensive crisis have been reported with duloxetine, especially in patients with pre-existing hypertension. Therefore, in patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended, especially during the first month of treatment. Duloxetine should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure. Caution should also be exercised when duloxetine is used with medicinal products that may impair its metabolism. 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 hemodialysis (creatinine clearance <30 ml/min).
Hemorrhage
There have been reports of bleeding abnormalities, such as ecchymoses, purpura and gastrointestinal hemorrhage with selective serotonin reuptake inhibitors (SSRIs) and serotonin/noradrenaline reuptake inhibitors (SNRIs), including duloxetine. Duloxetine may increase the risk of postpartum hemorrhage. 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.
Discontinuation of treatment
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt. In a clinical trial, adverse events seen on abrupt treatment discontinuation occurred in approximately 44% of patients treated with duloxetine and 24% of patients taking placebo.
The risk of withdrawal symptoms seen with SSRI's and SNRI's may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. 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.
Hyponatremia
Hyponatremia has been reported when administering Duloxetine, including cases with serum sodium lower than 110 mmol/l. Hypernatremia may be due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH). The majority of cases of hypernatremia 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 hypernatremia, such as elderly, cirrhotic, or dehydrated patients or patients treated with diuretics.

Depression, suicidal ideation and behavior

Although duloxetine is not indicated for the treatment of depression, its active ingredient (duloxetine) also exists as an antidepressant medicinal product. Depression is associated with an increased risk of suicidal thoughts, self -harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. 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 a greater risk of suicidal thoughts or suicidal behaviour and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant medicinal products in psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Cases of suicidal thoughts and suicidal behaviors have been reported during duloxetine therapy or early after treatment discontinuation. Physicians should encourage patients to report any distressing thoughts or feelings or depressive symptoms at any time. If while on duloxetine therapy, the patient develops agitation or depressive symptoms, specialised medical advice should be sought, as depression is a serious medical condition. If a decision to initiate antidepressant pharmacological therapy is taken, the gradual discontinuation of duloxetine is recommended.

Use in children and adolescents under 18 years of age

Duloxetine should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempts and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger), were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioral development are lacking.

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.

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.

Sexual dysfunction

Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction. There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRI.

Diabetic Peripheral Neuropathic Pain:

As with other medicinal products with similar pharmacological action (antidepressants), isolated cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation. Concerning risk factors for suicidality in depression. Physicians should encourage patients to report any distressing thoughts or feelings at any time

Elderly

Data on the use of duloxetine in elderly patients with major depressive disorder and generalized anxiety disorder are limited. Therefore, caution should be exercised when treating the elderly with the maximum dosage.

4.5 DRUG INTERACTIONS

Monoamine oxidase inhibitors (MAOIs): Due to the risk of serotonin syndrome, duloxetine should not be used in combination with nonselective irreversible monoamine oxidase inhibitors (MAOIs), or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping duloxetine before starting an MAOI.

The concomitant use of duloxetine 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 duloxetine.

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 duloxetine should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine.

CNS medicinal products: Caution is advised when duloxetine is taken in combination with other centrally acting medicinal products or substances, including alcohol and sedative medicinal products (e.g. benzodiazepines, morphinomimetics, antipsychotics, phenobarbital and 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 duloxetine is used concomitantly with serotonergic agents like SSRIs, SNRIs, tricyclic antidepressants like clomipramine or amitriptyline, MOAIs 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 metabolized by CYP1A2: The pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by co-administration with duloxetine (60 mg twice daily).

Medicinal products metabolized by CYP2D6: Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered at a dose of 60 mg twice daily with a single dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. The coadministration of duloxetine (40 mg twice daily) increases steady state AUC of tolterodine (2 mg twice daily) by 71 % but does not affect the pharmacokinetics of its active 5-hydroxyl metabolite and no dosage adjustment is recommended. Caution is advised if duloxetine is co-administered with medicinal products that are predominantly metabolised by CYP2D6 (risperidone, tricyclic antidepressants [TCAs] such as nortriptyline, amitriptyline, and imipramine) particularly if they have a narrow therapeutic index (such as flecainide, propafenone and metoprolol).

Oral contraceptives and other steroidal agents: Results of in vitro studies demonstrate that duloxetine does not induce the catalytic activity of CYP3A. Specific in vivo drug interaction studies have not been performed.

Anticoagulants and antiplatelet agents: Caution should be exercised when duloxetine is combined with oral anticoagulants or antiplatelet agents due to a potential increased risk of bleeding attributable to a pharmacodynamic interaction. Furthermore, increases in INR values have been reported when duloxetine was co-administered to patients treated with warfarin. However, concomitant administration of duloxetine with warfarin under steady state conditions, in healthy volunteers, as part of a clinical pharmacology study, did not result in a clinically significant change in INR from baseline or in the pharmacokinetics of R- or S-warfarin.

Effects of other medicinal products on duloxetine

Antacids and H2 antagonists: Co-administration of duloxetine with aluminium- and magnesium-containing antacids or 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 studies analyses have shown that smokers have almost 50% lower plasma concentrations of duloxetine compared with non-smokers.

4.6 USE IN SPECIAL POPULATIONS (SUCH AS PREGNANT WOMEN, LACTATING WOMEN, PAEDIATRIC PATIENTS, GERIATRIC PATIENTS ETC.)

Fertility

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

Pregnancy

There are no adequate data on the use of duloxetine in pregnant women. Studies in animals have shown reproductive toxicity at systemic exposure levels (AUC) of duloxetine lower than the maximum clinical exposure.

The potential risk for humans is unknown.

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 (inhibition of the re-uptake of serotonin).

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.
Observational data have provided evidence of an increased risk (less than 2 -fold) of postpartum haemorrhage following duloxetine exposure within the month prior to birth.
Duloxetine should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus. Women should be advised to notify their physician if they become pregnant, or intend to become pregnant, during therapy.

Breast feeding

Duloxetine is very weakly excreted into human milk based on a study of 6 lactating patients, who did not breast feed their children. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose. As the safety of duloxetine in infants is not known, the use of Duloxetine while breast-feeding is not recommended.

Pediatric Use

The safety and effectiveness of duloxetine have been established for treatment of generalized anxiety disorder (GAD) in patients 7 to 17 years of age and for treatment of juvenile fibromyalgia syndrome in patients 13 to 17 years of age. The safety and effectiveness of duloxetine have not been established in pediatric patients with major depressive disorder (MDD), diabetic peripheral neuropathic pain, or chronic musculoskeletal pain. Antidepressants increased the risk of suicidal thoughts and behavior in pediatric patients. Monitor all pediatric patients being treated with antidepressants for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of treatment, or at times of dosage changes.

Geriatric Use

The pharmacokinetics of duloxetine after a single dose of 40 mg were compared in healthy elderly females (65 to 77 years) and healthy middle-age females (32 to 50 years). There was no difference in the Cmax, but the AUC of duloxetine was somewhat (about 25%) higher and the half-life about 4 hours longer in the elderly females. Population pharmacokinetic analyses suggest that the typical values for clearance decrease by approximately 1% for each year of age between 25 to 75 years of age; but age as a predictive factor only accounts for a small percentage of between-patient variability. Dosage adjustment based on the age of the adult patient is not necessary.

Hepatic Impairment

Patients with clinically evident hepatic impairment have decreased duloxetine metabolism and elimination.

Severe Renal Impairment

Limited data are available on the effects of duloxetine in patients with end-stage renal disease (ESRD). Population PK analyses suggest that mild to moderate degrees of renal impairment (estimated CrCl 30-80 mL/min) have no significant effect on duloxetine apparent clearance.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. Duloxetine may be associated with sedation and dizziness. Patients should be instructed that if they experience sedation or dizziness they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 UNDESIRABLE EFFECTS

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).

Infections and infestations
Uncommon: Laryngitis
Immune system disorders
Rare: Anaphylactic reaction, Hyper-sensitivity disorder
Endocrine disorders
Rare: Hypothyroidism
Metabolism and nutrition disorders
Common: Appetite decreased
Uncommon: Hyperglycaemia (reported especially in diabetic patients)
Rare: Dehydration, Hyponatraemia, SIADH[6]
Psychiatric disorders
Common: Insomnia, Agitation, Libido decreased, Anxiety, Orgasm abnormal, abnormal dreams.
Uncommon: Suicidal ideation, sleep disorder, Bruxism, Disorientation, Apathy
Rare: Suicidal behaviour[5,7], Mania, Hallucinations, Aggression and anger[4]
Nervous system disorders
Very Common: Headache, Somnolence.
Common: Dizziness, lethargy, tremor and paraesthesia.
Uncommon: Myoclonus, Akathisia[7], Nervousness, Disturbance in attention, Dysgeusia, Dyskinesia, Restless legs syndrome, Poor quality sleep.
Rare: Serotonin syndrome[6], Convulsions[1], Psychomotor restlessness[6], Extra-pyramidal symptoms[6]
Eye disorders
Common: Blurred vision
Uncommon: Mydriasis, Visual impairment
Rare: Glaucoma
Ear and labyrinth disorders
Common: Tinnitus[1]
Uncommon: Vertigo, Ear pain
Cardiac disorders
Common: Palpitations
Uncommon: Tachycardia, Supra-ventricular arrhythmia, mainly atrial fibrillation
Vascular disorders
Common: Hypertension[3], Flushing
Uncommon: Syncope[2], Blood pressure increase[3,7], orthostatic hypotension[2], Peripheral coldness
Rare: Hypertensive crisis[3,6]
Respiratory, thoracic and mediastinal disorders
Common: Yawning
Uncommon: Throat tightness, Epistaxis,
Rare: Interstitial lung disease[10], Eosinophilic pneumonia[6]
Gastrointestinal disorders
Very Common: Nausea, Dry mouth

Common: Constipation, Diarrhoea, Abdominal pain, Vomiting, Dyspepsia and Flatulence.
Uncommon: Gastrointestinal haemorrhage[7]**,** Gastroenteritis**,** Eructation**,** Gastritis**,** Dysphagia
Rare: Stomatitis, Breath odour, Hematochezia**,** Microscopic colitis[9]
Hepato-biliary disorders
Uncommon: Hepatitis[3], Elevated liver enzymes (ALT, AST, alkaline phosphatase), Acute liver injury
Rare: Hepatic failure[6], Jaundice[6]
Skin and subcutaneous tissue disorders
Common: Sweating increased, Rash
Uncommon: Night sweats, Urticaria, Dermatitis contact, Cold sweat, increased tendency to bruise and photo sensitivity reactions.
Rare: Stevens - Johnson syndrome[6], Angio-neurotic oedema[6]
Very Rare: Cutaneous vasculitis
Musculoskeletal and connective tissue disorders
Common: Musculo-skeletal pain, Muscle spasm.
Uncommon: Muscle twitching and Muscle tightness.
Rare: Trismus
Renal and urinary disorders
Common: Dysuria, pollakiuria
Uncommon: Urinary hesitation, Urinary retention, Nocturia, Polyuria, Urine flow decreased.
Rare: Urine odour abnormal.
Unknown: hyponatremia.
Reproductive system and breast disorders
Common: Erectile dysfunction, Ejaculation disorder, Ejaculation delayed.
Uncommon: Gynecological hemorrhage, menstrual disorder, sexual dysfunction and testicular pain.
Rare: Menopausal symptoms, galactorrhea, hyperprolactinemia, postpartum haemorrhage[6]
General disorders and administration site conditions
Very Common: Falls[8], Fatigue.
Uncommon: Chest pain[7], Feeling abnormal, Feeling cold, Thirst, chills, Malaise, Feeling hot and gait disturbance
Investigations
Common: Weight decrease.
Uncommon: Weight increase, Blood potassium increased, Blood creatine phosphokinase increased.
Rare: 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

Reporting of suspected adverse reactions
Health care professionals, patients/consumers are advised to closely monitor the possibility of the above ADRs associated with the use of the above drugs. If such reactions are encountered and for any product related complaints, please write to **webmasterindia@abbott.com**

4.9 OVERDOSE
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, hemoperfusion, and exchange perfusion are unlikely to be beneficial.

5. PHARMACOLOGICAL PROPERTIES

5.1 MECHANISM OF ACTION
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.

5.2 PHARMACODYNAMIC PROPERTIES
In animal studies, increased levels of 5-HT and NE in the sacral spinal cord, lead to increased urethral tone via enhanced pudendal nerve stimulation to the urethral striated sphincter muscle only during the storage phase of the micturition cycle. A similar mechanism in women is believed to result in stronger urethral closure during urine storage with physical stress that could explain the efficacy of duloxetine in the treatment of women with SUI.

5.3 PHARMACOKINETIC PROPERTIES

Absorption:

Duloxetine is well absorbed after oral administration with a Cmax occurring 6 hours post dose. The absolute oral bioavailability of duloxetine ranged from 32% to 80% (mean of 50%). Food delays the time to reach the peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11 %). These changes do not have any clinical significance.

Distribution:
Duloxetine is approximately 96% bound to human plasma proteins. Duloxetine binds to both albumin and alpha-l acid glycoprotein. Protein binding is not affected by renal or hepatic impairment.

Metabolism:
Duloxetine is extensively metabolized and the metabolites are excreted principally in urine. Both cytochromes P450-2D6 and 1A2 catalyze the formation of the two major metabolites glucuronide conjugate of 4-hydroxy duloxetine and sulphate conjugate of 5-hydroxy 6-methoxy duloxetine. Based upon in vitro studies, the circulating metabolites of duloxetine are considered pharmacologically inactive. The pharmacokinetics of duloxetine in patients who are poor metabolisers with respect to CYP2D6 has not been specifically investigated. Limited data suggest that the plasma levels of duloxetine are higher in these patients.

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

6. NONCLINICAL PROPERTIES

6.1 ANIMAL TOXICOLOGY OR PHARMACOLOGY
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 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 pre/postnatal toxicity study in the rat, duloxetine induced adverse behavioural effects in the offspring at systemic exposure levels below maximum clinical exposure (AUC).
Studies in juvenile rats reveal transient effects on neurobehavior, 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.

7. DESCRIPTION

Delok® 20
DELOK 20 is supplied for oral administration, as a delayed release capsule of Duloxetine. Each hard gelatin capsule of DELOK contains Duloxetine Hydrochloride equivalent to Duloxetine 20 mg (As Enteric coated pallets).

Delok® 30
DELOK 30 is supplied for oral administration, as a delayed release capsule of Duloxetine. Each hard gelatin capsule of DELOK contains Duloxetine Hydrochloride equivalent to Duloxetine 30 mg (As Enteric coated pallets).

8. PHARMACEUTICAL PARTICULARS

8.1 INCOMPATIBILITIES
Not applicable.

8.2 SHELF-LIFE
Refer Pack

8.3 PACKING INFORMATION
Refer Pack

8.4 STORAGE CONDITION AND HANDLING INSTRUCTIONS
Refer Pack

9. PATIENT COUNSELLING INFORMATION
Suicidal thoughts and behaviors:
Advise patients, their families, and their caregivers to look for the emergence of suicidal ideation and behavior, especially during treatment and when the dose is adjusted up or down and instruct them to report such symptoms to their healthcare provided.
Duloxetine should be swallowed whole and should not be chewed or crushed, nor should the capsule be opened and its contents be sprinkled on food or mixed with liquids. All of these might affect the enteric coating.
Hepatotoxicity
Inform patients that severe liver problems, sometimes fatal, have been reported in patients treated with duloxetine. Instruct patients to talk to their healthcare provider if they develop itching, right upper belly pain, dark urine, or yellow skin/eyes while taking duloxetine, which may be signs of liver problems. Instruct patients to talk to their healthcare provider about their alcohol consumption. Use of duloxetine with heavy alcohol intake may be associated with severe liver injury.
Alcohol

Although duloxetine does not increase the impairment of mental and motor skills caused by alcohol, use of duloxetine concomitantly with heavy alcohol intake may be associated with severe liver injury. For this reason, duloxetine should not be prescribed for patients with substantial alcohol use.

Orthostatic Hypotension, Falls and Syncope

Advise patients of the risk of orthostatic hypotension, falls and syncope, especially during the period of initial use and subsequent dose escalation, and in association with the use of concomitant drugs that might potentiate the orthostatic effect of duloxetine.

Serotonin Syndrome

Caution patients about the risk of serotonin syndrome with the concomitant use of duloxetine and other serotonergic agents including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, amphetamines, and St. John's Wort. Advise patients of the signs and symptoms associated with serotonin syndrome that may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular changes (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Caution patients to seek medical care immediately if they experience these symptoms.

Abnormal Bleeding

Caution patients about the concomitant use of duloxetine and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding.

Severe Skin Reactions

Caution patients that duloxetine may cause serious skin reactions. This may need to be treated in a hospital and may be life-threatening. Counsel patients to call their doctor right away or get emergency help if they have skin blisters, peeling rash, sores in their mouth, hives, or any other allergic reactions.

Discontinuation of Treatment

Instruct patients that discontinuation of duloxetine may be associated with symptoms such as dizziness, headache, nausea, diarrhea, paresthesia, irritability, vomiting, insomnia, anxiety, hyperhidrosis, and fatigue, and should be advised not to alter their dosing regimen, or stop taking duloxetine without consulting their physician.

Activation of Mania or Hypomania

Adequately screen patients with depressive symptoms for risk of bipolar disorder (e.g. family history of suicide, bipolar disorder, and depression) prior to initiating treatment with duloxetine. Advise patients to report any signs or symptoms of a manic reaction such as greatly increased energy, severe trouble sleeping, racing thoughts, reckless behavior, talking more or faster than usual, unusually grand ideas, and excessive happiness or irritability.

Angle-Closure Glaucoma

Advise patients that taking duloxetine can cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle-closure glaucoma. Pre-existing glaucoma is almost always open-angle glaucoma because angle-closure glaucoma, when diagnosed, can be treated definitively with iridectomy. Open-angle glaucoma is not a risk factor for angle-closure glaucoma.

Patients may wish to be examined to determine whether they are susceptible to angle-closure, and have a prophylactic procedure (e.g., iridectomy), if they are susceptible.

Seizures

Advise patients to inform their physician if they have a history of seizure disorder.

Effects on Blood Pressure

Caution patients that duloxetine may cause an increase in blood pressure.

Concomitant Medications

Advise patients to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter medications, since there is a potential for interactions.

Hyponatremia

Advise patients that hyponatremia has been reported as a result of treatment with SNRIs and SSRIs, including duloxetine. Advise patients of the signs and symptoms of hyponatremia.

Concomitant Illnesses

Advise patients to inform their physicians about all of their medical conditions.

Duloxetine is in a class of medicines that may affect urination. Instruct patients to consult with their healthcare provider if they develop any problems with urine flow.

Pregnancy

Advise pregnant women to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with duloxetine.

Advise patients that duloxetine use during the month before delivery may lead to an increased risk for postpartum hemorrhage and may increase the risk of neonatal complications requiring prolonged hospitalization, respiratory support, and tube feeding.

Advise pregnant women that there is a risk of relapse with discontinuation of antidepressants.

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to duloxetine during pregnancy.

Lactation

Advise breastfeeding women using duloxetine to monitor infants for sedation, poor feeding and poor weight gain and to seek medical care if they notice these signs.

Pediatric Use

Safety and efficacy of duloxetine in patients 7 to 17 years of age have been established for the treatment of GAD. The types of adverse reactions observed with duloxetine in children and adolescents were generally similar to those observed in adults. The safety and effectiveness of duloxetine have not been established in pediatric patients less than 18 years of age with other indications.

Interference with Psychomotor Performance

Any psychoactive drug may impair judgment, thinking, or motor skills. Although in controlled studies duloxetine has not been shown to impair psychomotor performance, cognitive function, or memory, it may be associated with sedation and dizziness. Therefore, caution patients about operating hazardous machinery including automobiles, until they are reasonably certain that duloxetine therapy does not affect their ability to engage in such activities.

Urinary Hesitation and Retention

Duloxetine is in a class of medicines that may affect urination. Instruct patients to consult with their healthcare provider if they develop any problems with urine flow.

10. DETAILS OF MANUFACTURER
Refer Pack for manufacturer details.

MARKETED BY:
Abbott Healthcare Pvt. Ltd.
Angel Space, Bldg. D-4, Gala No. 1 to 6 &
11 to 16 Ground Floor, 101 to 106 &
111 to 116 First Floor, 201 to 206 & 211 to 216
2nd Floor, Pimplas, Dist. Thane, Bhiwandi - 421 302, India.

11. DETAILS OF PERMISSION OR LICENCE NUMBER
Refer Pack for Permission/License details

12. DATE OF REVISION
Version 4.0 Dated 12th Sep 2023