120x300mm

120x300mm

Dlexet®

(Duloxetine)

Highnoon

COMPOSITION
Dlexet 20mg Capsule: Each capsule contains:
Duloxetine as HCl (delayed-release pellets)20mg

Dlexet 30mg Capsule: Each capsule contains:
Duloxetine as HCl (delayed-release pellets)30mg

DESCRIPTION
Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor (SNRI) for oral administration.

MECHANISM OF ACTION
Duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake. Duloxetine has no significant affinity for dopaminergic, adrenergic, cholinergic, histaminergic, opioid, glutamate, and GABA receptors *in vitro*. Duloxetine does not inhibit monoamine oxidase (MAO). Duloxetine is in a class of drugs known to affect urethral resistance. Although the exact mechanisms of the antidepressant, central pain inhibitory and anxiolytic actions of duloxetine in humans are unknown, these actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS.

PHARMACOKINETICS
Duloxetine is well absorbed from the gastrointestinal tract and peak plasma concentrations occur about 16 hours after an oral dose. Food delays the time to reach peak concentrations to 10 hours. Protein binding is about 96%mainly albumin and alpha1 acid glycoprotein. Duloxetine is extensively metabolized by cytochrome P450 isoenzymes CYP1A2 and CYP2D6; two major, but inactive metabolite are formed, 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulphate. These and other metabolites are mainly excreted in the urine, about 20% excreted in the faeces. Less than 1% of a dose is excreted in the urine as unchanged duloxetine. The elimination half-life of duloxetine is 8 to 17 hours with an average of about 12 hours. Duloxetine is distributed into breast milk.

INDICATIONS AND USAGE
It is indicated for the treatment of;

- Major depressive disorder in adults
- Generalized anxiety disorder in adults and pediatric patients 7 years of age and older
- Diabetic peripheral neuropathic pain in adults
- Fibromyalgia in adults and pediatric patients 13 years of age and older
- Chronic musculoskeletal pain in adults

DOSAGE AND ADMINISTRATION

- The recommended starting dosage in adults with Major Depressive Disorder (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 dlexet (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.
- The recommended dosage for Generalized Anxiety Disorder (GAD) in most adults less than 65 years of age, is to initiate dlexet (duloxetine) 60 mg once daily. For some patients, it may be desirable to start at 30 mg once daily for 1 week, to allow patients to adjust to dlexet (duloxetine) before increasing to 60 mg once daily. While a 120 mg once daily dosage was shown to be effective, there is no evidence that doses greater than 60 mg/day confer additional benefit. Nevertheless, if a decision is made to increase the dosage beyond 60 mg once daily, increase dosage in increments of 30 mg once daily. Periodically reassess to determine the continued need for maintenance treatment and the appropriate dosage for such treatment.
- The recommended dosage for GAD in geriatric patients is to initiate dlexet (duloxetine) at a dosage of 30 mg once daily for 2 weeks before considering an increase to the target dose of 60 mg/day. Thereafter, patients may benefit from doses above 60 mg once daily. If a decision is made to increase the dose beyond 60 mg once daily, increase dose in increments of 30 mg once daily. The maximum dose studied was 120 mg per day.
- The recommended dosage for GAD in pediatric patients 7 years to 17 years of age is to initiate dlexet (duloxetine) at a dosage of 30 mg once daily for 2 weeks before considering an increase to 60 mg once daily. The recommended dosage range is 30 to 60 mg once daily. Some patients may benefit from dosages above 60 mg once daily. If a decision is made to increase the dose beyond 60 mg once daily, increase dosage in increments of 30 mg once daily. The maximum dose studied was 120 mg per day.
- The recommended dosage of dlexet (duloxetine) for the treatment of Peripheral Neuropathic Pain in adults is 60 mg once daily. There is no evidence that doses higher than 60 mg once daily confer additional significant benefit and the higher dosage is clearly less well tolerated. For patients for whom tolerability is a concern, a lower starting dose may be considered. Since diabetes is frequently complicated by renal disease, consider a lower starting dosage and gradual increase in dosage for patients with renal impairment.
- The recommended dosage of dlexet (duloxetine) for the treatment of Fibromyalgia in adults is 60 mg once daily. Begin treatment at 30 mg once daily for 1 week, to allow patients to adjust to dlexet (duloxetine) before increasing to 60 mg once daily. Some patients may respond to the starting dosage. There is no evidence that dosages greater than 60 mg/day confer additional benefit, even in patients who do not respond to a 60 mg/day dosage, and higher dosages were associated with a higher rate of adverse reactions.
- The recommended dosage of dlexet (duloxetine) for the treatment of Fibromyalgia in pediatric patients 13-17 years of age is 30 mg once daily. The dosage may be increased to 60 mg once daily based on response and tolerability.
- The recommended dosage of dlexet (duloxetine) for the treatment of chronic musculoskeletal pain in adults is 60 mg once daily. Begin treatment at 30 mg once daily for one week, to allow patients to adjust to dlexet (duloxetine) before increasing to 60 mg once daily. There is no evidence that higher dosages confer additional benefit, even in patients who do not respond to a 60 mg once daily dosage, and higher dosages are associated with a higher rate of adverse reactions.
  Administer Dlexet (Duloxetine) orally (with or without meals) and swallow whole. Do not chew or crush, and do not open the delayed-release capsule and sprinkle its contents on food or mix with liquids because these actions might affect the enteric coating. If a dose of Dlexet (Duloxetine) is missed, take the missed dose as soon as it is remembered. If it is almost time for the next dose, skip the missed dose and take the next dose at the regular time. Do not take two doses of Dlexet (Duloxetine) at the same time.

CONTRAINDICATIONS
Duloxetine is contraindicated in:

- The use of MAOIs intended to treat psychiatric disorders with duloxetine or within 5 days of stopping treatment with duloxetine is contraindicated because of an increased risk of serotonin syndrome.
- The use of duloxetine within 14 days of stopping an MAOI intended to treat psychiatric disorders is contraindicated.
- Starting duloxetine in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome.

ADVERSE REACTIONS
The reported adverse events of duloxetine are; suicidal thoughts and behaviors in children, adolescents, and young adults, hepatotoxicity, orthostatic hypotension, peripheral coldness, falls, syncope, serotonin syndrome, increased risk of bleeding, severe skin reactions, mania, hypomania, angle closure glaucoma, seizures, increases in blood pressure, hyponatremia, urinary hesitation and retention, sexual dysfunction, ejaculation delayed, libido decreased, orgasm abnormal, anorgasmia, menopausal disorder, nausea, vomiting, diarrhea, dyspepsia, flatulence; dysphagia, eructation, gastritis, gastrointestinal hemorrhage, halitosis, and stomatitis, gastric ulcer, constipation, dizziness, tremor, insomnia, anxiety, agitation, paresthesia, dysgeusia, lethargy, hypoesthesia, disturbance in attention, dyskinesia, myoclonus, poor quality sleep, muscle twitching, dysarthria, somnolence, flushing, hot flush, headache, fatigue, decreased appetite, dry mouth, hyperhidrosis, abdominal pain, palpitation, vision blurred, yawning, oropharyngeal pain, throat tightness, cough, nasopharyngitis, upper respiratory tract infection, influenza, musculoskeletal pain, muscle spasm, muscle tightness, raised alkaline phosphatase, high bicarbonate, high cholesterol, and abnormal (high or low) potassium, myocardial infarction, tachycardia, takotsubo cardiomyopathy, vertigo, ear pain, tinnitus, hypothyroidism, diplopia, dry eye, visual impairment, chills, rigors, feeling abnormal, feeling hot and/or cold, malaise, thirst, gait disturbance, gastroenteritis, laryngitis, weight increase, weight decrease, dehydration, hyperlipidemia, dyslipidemia, abnormal dreams, apathy, bruxism, disorientation, confusional state, irritability, mood swings, suicide attempt, urinary frequency, dysuria, micturition urgency, nocturia, polyuria, urine odor abnormal, pruritus, cold sweat, dermatitis contact, erythema, increased tendency to bruise, night sweats, photosensitivity reaction, ecchymosis, rash, trismus, angioneurotic edema, colitis (microscopic or unspecified), cutaneous vasculitis (sometimes associated with systemic involvement), extrapyramidal disorder, galactorrhea, gynecological bleeding, hallucinations, hyperglycemia, hyperprolactinemia, hypersensitivity, hypertensive crisis, restless legs syndrome, urticaria, and supraventricular arrhythmia,

DRUG INTERACTIONS
Drug interaction associated with duloxetine are;

- Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.
- Coadministration of duloxetine with fluvoxamine is a potent CYP1A2 inhibitor, there is an increase in duloxetine t1/2, Cmax, and AUC.
- Concomitant use of duloxetine with paroxetine increased the concentration of duloxetine AUC, and greater degrees of inhibition are expected with higher doses of paroxetine. Similar effects would be expected with other potent CYP2D6 inhibitors (e.g., fluoxetine, quinidine).
- Concomitant administration of duloxetine with fluvoxamine, a potent CYP1A2 inhibitor, to CYP2D6 poor metabolizer resulted in an increase in duloxetine AUC and Cmax.
- Serotonin release by platelets plays an important role in hemostasis. Use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are co-administered with warfarin. Concomitant administration of warfarin did not significantly change INR. Because of the potential effect of duloxetine on platelets, patients receiving warfarin therapy should be carefully monitored when duloxetine is initiated or discontinued.
- Under steady-state conditions for duloxetine and lorazepam, the pharmacokinetics of duloxetine were not affected by co-administration.
- Under steady-state conditions for duloxetine and temazepam, the pharmacokinetics of duloxetine were not affected by co-administration.
- Caution is advised in using duloxetine in patients with conditions that may slow gastric emptying (e.g., some diabetics). Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. However, co-administration of duloxetine with aluminum-and magnesium-containing antacids or duloxetine with famotidine, had no significant effect on the rate or extent of duloxetine absorption. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption.
- Duloxetine does not induce CYP1A2 activity. Therefore, an increase in the metabolism of CYP1A2 substrates (e.g., theophylline, caffeine) resulting from induction is not anticipated. Duloxetine is an inhibitor of the CYP1A2, there is an increase in AUC when co-administered with duloxetine.
- Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered in conjunction with desipramine, a CYP2D6 substrate, the AUC of desipramine increased.
- Drugs metabolized by CYP2C9, demonstrate that duloxetine does not inhibit activity. The pharmacokinetics of S-warfarin, a CYP2C9 substrate, were not significantly affected by duloxetine.
- Drugs metabolized by CYP3A, demonstrate that duloxetine does not inhibit or induce CYP3A activity. Therefore, an increase or decrease in the metabolism of CYP3A substrates (e.g., oral contraceptives and other steroidal agents) resulting from induction or inhibition is not anticipated.
- Drugs metabolized by CYP2C19, demonstrate that duloxetine does not inhibit CYP2C19 activity at therapeutic concentrations.
- Inhibition of the metabolism of CYP2C19 substrates is therefore not anticipated, although clinical studies have not been performed.
- Do not start duloxetine in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered. In patient already receiving duloxetine therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, duloxetine should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 5 days or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with duloxetine may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue.
- The concomitant use of serotonergic drugs (including other SNRIs, SSRIs, triptans, tricyclic antidepressants, opioids, lithium, buspirone, amphetamines, tryptophan, and St. John's Wort) with duloxetine increases the risk of serotonin syndrome. Monitor patients for signs and symptoms of serotonin syndrome, particularly during treatment initiation and dosage increases. If serotonin syndrome occurs, consider discontinuation of duloxetine and/or concomitant serotonergic drugs.
- When duloxetine and ethanol were administered several hours apart so that peak concentrations of each would coincide, duloxetine did not increase the impairment of mental and motor skills caused by alcohol.
- Duloxetine should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action.
- Because duloxetine is highly bound to plasma protein, administration of duloxetine to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse reactions.

WARNINGS AND PRECAUTIONS

- Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.
  Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.
  If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that discontinuation can be associated with certain symptoms for descriptions of the risks of discontinuation of duloxetine.
  Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers.
- Prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that duloxetine is not approved for use in treating bipolar depression.
- There have been reports of hepatic failure, sometimes fatal, in patients treated with duloxetine. These cases have been presented as hepatitis with abdominal pain, hepatomegaly, and elevation of transaminase levels to more than twenty times the upper limit of normal (ULN) with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Duloxetine should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established. Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported. Patients with chronic liver disease or cirrhosis elevated transaminases, bilirubin, and alkaline phosphatase have also occurred.
  It is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease. Duloxetine should not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.
- Orthostatic hypotension, falls, and syncope have been reported in patients treated with the recommended duloxetine dosages. Syncope and orthostatic hypotension tend to occur within the first week of therapy but can occur at any time during duloxetine treatment, particularly after dose increases. The risk of falling appears to be related to the degree of orthostatic decrease in blood pressure (BP) as well as other factors that may increase the underlying risk of falls. The risk of BP decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as antihypertensives) or are potent CYP1A2 inhibitors and in patients taking duloxetine at doses above 60 mg daily. Consideration should be given to dose reduction or discontinuation of duloxetine in patients who experience symptomatic orthostatic hypotension, falls and/or syncope during duloxetine therapy.
- Risk of falling also appeared to be proportional to a patient's underlying risk for falls and appeared to increase steadily with age. As geriatric patients tend to have a higher underlying risk for falls due to a higher prevalence of risk factors such as use of multiple medications, medical comorbidities and gait disturbances, the impact of increasing age by itself is unclear. Falls with serious consequences including fractures and hospitalizations have been reported with duloxetine use.
- Serotonin-norepinephrine reuptake inhibitors (SNRIs), including duloxetine, can precipitate serotonin syndrome, a potentially life-threatening condition. The risk is increased with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, meperidine, methadone, tryptophan, buspirone, amphetamines, and St. John's Wort) and with drugs that impair metabolism of serotonin, i.e., MAOIs. Serotonin syndrome can also occur when these drugs are used alone. Serotonin syndrome signs and symptoms 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 symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The concomitant use of duloxetine with MAOIs is contraindicated. In addition, do not initiate duloxetine in a patient being treated with MAOIs such as linezolid or intravenous methylene blue. If it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking duloxetine, discontinue duloxetine before initiating treatment with the MAOI.
  Monitor all patients taking duloxetine for the emergence of serotonin syndrome. Discontinue treatment with duloxetine and any concomitant serotonergic agents immediately if the above symptoms occur and initiate supportive symptomatic treatment. If concomitant use of duloxetine with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome and monitor for symptoms.
- Drugs that interfere with serotonin reuptake inhibition, including duloxetine, may increase the risk of bleeding events. Bleeding events related to SSRI and SNRI use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anti□coagulants may add to this risk. Inform patients about the risk of increased bleeding associated with the concomitant use of duloxetine and NSAIDs, aspirin, or other drugs that affect coagulation.
- Severe skin reactions, including erythema multiforme and Stevens-Johnson Syndrome (SJS), can occur with duloxetine. Duloxetine should be discontinued at the first appearance of blisters, peeling rash, mucosal erosions, or any other sign of hypersensitivity if no other etiology can be identified.
- Discontinuation symptoms have been systematically evaluated in patients taking duloxetine. The reported symptoms are dizziness, headache, nausea, diarrhea, paresthesia, irritability, vomiting, insomnia, anxiety, hyperhidrosis, and fatigue. There have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe. Patients should be monitored for these symptoms when discontinuing treatment with duloxetine. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered.
- Activation of mania or hypomania was reported in a small proportion of patients with mood disorders who were treated with other marketed drugs effective in the treatment of major depressive disorder. As with these other agents, duloxetine should be used cautiously in patients with a history of mania.
- The pupillary dilation that occurs following use of many antidepressant drugs including duloxetine may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.
- Duloxetine has not been systematically evaluated in patients with a seizure disorder and should be prescribed with care in patients with a history of a seizure disorder.
- Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment with duloxetine.
- Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism. Co-administration of duloxetine with potent CYP1A2 and CYP2D6 inhibitors should be avoided.
- Use of duloxetine concomitantly with heavy alcohol intake may be associated with severe liver injury. Duloxetine should not be prescribed for patients with substantial alcohol use.
- Duloxetine should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action.
- Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including duloxetine. Geriatric patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk. Discontinuation of duloxetine should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. More severe and/or acute cases have been associated with hallucination, syncope, seizure, coma, respiratory arrest, and death.
- Caution is advised in using duloxetine in patients with conditions that may slow gastric emptying (e.g., some diabetics). Duloxetine has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable coronary artery disease.
- Avoid use in patients with chronic liver disease or cirrhosis.
- Avoid use in patients with severe renal impairment, GFR <30 mL/minute. Increased plasma concentration of duloxetine, and especially of its metabolites, occurred in patients with end-stage renal disease (requiring dialysis).
- Duloxetine treatment worsened glycemic control in some patients with diabetes.
- Duloxetine is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during treatment with duloxetine, consideration should be given to the possibility that they might be drug related.
- Use of SNRIs, including duloxetine, may cause symptoms of sexual dysfunction. In male patients, SNRI use may result in ejaculatory delay or failure, decreased libido, and erectile dysfunction. In female patients, SNRI use may result in decreased libido and delayed or absent orgasm.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are risks associated with untreated depression and fibromyalgia in pregnancy, and with exposure to SNRIs and SSRIs, including duloxetine, during pregnancy.
Women who discontinue antidepressants during pregnancy are more likely to experience a relapse of major depression than women who continue antidepressants. Consider the risk of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum. Pregnant women with fibromyalgia are at increased risk for adverse maternal and infant outcomes including preterm premature rupture of membranes, preterm birth, small for gestational age, intrauterine growth restriction, placental disruption, and venous thrombosis. It is not known if these adverse maternal and fetal outcomes are a direct result of fibromyalgia or other comorbid factors. Neonates exposed to duloxetine and other SNRIs or SSRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremors, jitteriness, irritability, and constant crying. These findings are consistent with either a direct toxic effect of the SNRIs or SSRIs, or possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome.

Breast-feeding
Risk Summary.
There are reports of sedation, poor feeding, and poor weight gain in infants exposed to duloxetine through breast milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for duloxetine and any potential adverse effects on the breastfed child from duloxetine or from the underlying maternal condition. Infants exposed to duloxetine should be monitored for sedation, poor feeding and poor weight gain.

Pediatric Use
The safety and effectiveness of duloxetine have been established for the 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. The safety and effectiveness of duloxetine for the treatment of GAD in pediatric patients less than 7 years of age have not been established. The safety and effectiveness of duloxetine for the treatment of fibromyalgia in patients less than 13 years of age have not been established.

Geriatric Use
There are no overall differences in safety or effectiveness that were generally observed between geriatric patients and younger adult patients. A higher rate of fall has been reported with duloxetine and the increased risk appears to be proportional to a patient's underlying risk for falls. The underlying risk appears to increase steadily with age. As geriatric patients tend to have a higher prevalence of risk factors for falls such as medications, medical comorbidities and gait disturbances, the impact of increasing age by itself on falls during duloxetine treatment is unclear. Falls with serious consequences including bone fractures and hospitalizations have been reported with duloxetine use. 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).

DRUG ABUSE AND DEPENDENCE
Abuse
Duloxetine has not been systematically studied in humans for its potential for abuse, there was no indication of drug-seeking behavior. Physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of duloxetine (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Dependence
Duloxetine did not demonstrate dependence-producing potential in animals.

OVERDOSAGE
Fatal outcomes have been reported for acute duloxetine overdoses, primarily with mixed overdoses, but also with duloxetine only. Signs and symptoms of overdose (duloxetine alone or with mixed drugs) included somnolence, coma, serotonin syndrome, seizures, syncope, tachycardia, hypotension, hypertension, and vomiting.
There is no specific antidote to a duloxetine overdosage, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. In case of acute overdose with duloxetine, treatment should consist of those general measures employed in the management of overdose with any drug, such as assuring an adequate airway, oxygenation, and ventilation and monitoring cardiac rhythm and vital signs. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Induction of emesis is not recommended.
Activated charcoal may be useful in limiting absorption of duloxetine from the gastrointestinal tract. Due to the large volume of distribution of duloxetine, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be beneficial. In managing overdose, the possibility of multiple drug involvement should be considered. A specific caution involves patients who overdose with duloxetine and tricyclic antidepressants.

DOSAGE & INSTRUCTIONS
To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30ºC. Keep in a dry place. Protect from Light.

PRESENTATION
Dlexet 20mg Capsules:
Alu. Alu. Blister Pack of 1 x 10's.
Dlexet 30mg Capsules:
Alu. Alu. Blister Pack of 1 x 10's.

ڈلیکسٹ®

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