Dostax Capsules

ڈوسٹیکس کیپسولز

COMPOSITION: *Each capsule contains:* Duloxetine (as HCl) Enteric Coated Pellets*.....30 & 60 mg, respectively.

DESCRIPTION: Duloxetine hydrochloride is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) for oral administration. Its chemical designation is (+)-(S)-N-methyl-Y-(1-naphthyloxy) - 2-thiophenepropylamine hydrochloride. The empirical formula is $C_{18}H_{19}NOS \cdot HCl$ and has a molecular weight of 333.88.

PHARMACOLOGY: Pharmacodynamics: 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). Pharmacokinetics: Orally administered duloxetine hydrochloride is well absorbed. There is a median 2 hour lag until absorption begins (Tlag), with maximal plasma concentrations (C_{max}) of duloxetine occurring 6 hours post dose. Food does not affect the C_{max} of duloxetine, but delays the time to reach peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (AUC) by about 10%. There is a 3 hour delay in absorption and a one-third increase in apparent clearance of duloxetine after an evening dose as compared to a morning dose. The apparent volume of distribution averages about 1640 L. Duloxetine is highly bound (>90%) to proteins in human plasma, binding primarily to albumin and alpha1-acid glycoprotein. Duloxetine has an elimination half-life of about 12 hours (range 8 to 17 hours) and its pharmacokinetics is dose proportional over the therapeutic range. Steady-state plasma concentrations are typically achieved after 3 days of dosing. Elimination of duloxetine is mainly through extensive hepatic metabolism involving two P450 isozymes, CYP1A2 and CYP2D6. Metabolites found in plasma include 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate; others have been identified in the urine. The major circulating metabolites have not been shown to contribute significantly to the pharmacologic activity of duloxetine. Only trace (<1% of the dose) amounts of unchanged duloxetine are present in the urine. Most (about 70%) of the duloxetine dose appears in the urine as metabolites of duloxetine; about 20% is excreted in the feces.

INDICATIONS: • Major Depressive Disorder (MDD): DOSTAX is indicated for the acute and maintenance treatment of MDD. • Generalized Anxiety Disorder (GAD). • Diabetic Peripheral Neuropathic Pain (DPNP). • Fibromyalgia.

CONTRAINDICATIONS: *Monoamine Oxidase Inhibitors:* Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs. Uncontrolled Narrow-Angle Glaucoma: In clinical trials, duloxetine hydrochloride use was associated with an increased risk of mydriasis; therefore, its use should be avoided in patients with uncontrolled narrow-angle glaucoma.

POSSIBLE ADVERSE EFFECTS: The commonly encountered side effects are nausea, headache, dry mouth, fatigue, insomnia, dizziness, somnolence, constipation, diarrhea, decreased appetite and hyperhidrosis. Small mean increases from baseline to endpoint in ALT, AST, CPK, and alkaline phosphatase have also been observed.

DRUG INTERACTIONS: Inhibitors of CYP1A2: Coadministration with fluvoxamine, cimetidine and quinolone antibiotic, potent CYP1A2 inhibitors, resulted in increase in AUC approximately 6-fold, the C_{max} was increased about 2.5-fold and duloxetine t1/2 was increased approximately 3-fold. Inhibitors of CYP2D6: Concomitant use of duloxetine (40 mg once daily) with paroxetine (20 mg once daily) increased the concentration of duloxetine AUC by about 60%. Similar effects are expected with fluoxetine and quinidine. Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin): Concurrent use of duloxetine with NSAIDs and aspirin may potentiate the risk of upper gastrointestinal bleeding. Patients receiving warfarin therapy should be carefully monitored when duloxetine is initiated or discontinued. Drugs that Affect Gastric Acidity: Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. *Drugs Metabolized by CYP1A2:* Duloxetine is an inhibitor of the CYP1A2 isoform in in vitro studies and in two clinical studies the average (90% confidence interval) increase in theophylline AUC was 7% and 20% when co-administered with duloxetine (60 mg twice daily). Drugs Metabolized by CYP2D6: When duloxetine was administered in conjunction with a single 50 mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. Serotonergic Drugs: Based on the mechanism of action of SNRIs and SSRIs, including duloxetine, and the potential for serotonin syndrome, caution is advised when duloxetine is co-administered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid, lithium and tramadol. The concomitant use of duloxetine with other SSRIs, SNRIs or tryptophan is not recommended. Triptans: If concomitant treatment of duloxetine with a triptan is clinically warranted, careful observation of the patient is advised. Drugs Highly Bound to Plasma Protein: 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. CNS Acting Drugs: Given the primary CNS effects of duloxetine, it should be used with caution when it is taken in combination with or substituted for other centrally acting drugs including certain antidepressants (tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine) and phenothiazines. Alcohol: Use of duloxetine concomitantly with heavy alcohol intake may be associated with severe liver injury.

WARNINGS: Clinical Worsening & Suicide Risk: All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behaviour, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Families and caregivers should immediately report any unusual changes in behaviour or emergence of suicidality to the doctor. It should also be noted that duloxetine is not approved for use in treating bipolar depression. Hepatoxicity: There have been reports of hepatic failure, sometimes fatal, in patients treated with duloxetine, therefore it 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. Orthostatic Hypotension & Syncope: Orthostatic hypotension and syncope have been reported with therapeutic doses of duloxetine. Consideration should be given to discontinuing duloxetine in patients who experience symptomatic orthostatic hypotension and/or syncope during duloxetine therapy. Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions: The development of a potentially life-threatening serotonin syndrome (agitation, hallucinations, coma, tachycardia, hyperthermia, labile blood pressure, hyper-reflexia, incoordination, nausea, vomiting, diarrhea) or Neuroleptic Malignant Syndrome (hyperthermia, muscle rigidity, autonomic instability, rapid fluctuation of vital signs and mental status changes)-like reactions have been reported with SNRIs and SSRIs alone, including duloxetine treatment. The concomitant use of duloxetine with MAOIs intended to treat depression is contraindicated. If concomitant treatment of duloxetine with a 5-hydroxytryptamine receptor

agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of duloxetine with serotonin precursors (such as tryptophan) is not recommended. Abnormal Bleeding: SSRIs and SNRIs, including duloxetine, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anti-coagulants may add to this risk. Activation of Mania/Hypomania: Activation of mania or hypomania has been 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. Discontinuation of 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. Subsequently, the physician may continue decreasing the dose but at a more gradual rate. Seizures: Duloxetine should be prescribed with care in patients with a history of a seizure disorder. *Effect on Blood Pressure:* Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment. *Hyponatremia:* Discontinuation of duloxetine should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Urinary Hesitation & Retention: 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. Pregnancy: There are no adequate and well-controlled studies in pregnant women; therefore, duloxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Pediatric Use: Safety and effectiveness in the pediatric population have not been established. Lactation: Safety of duloxetine in infants is not known; nursing while on duloxetine is not recommended.

DOSAGE & ADMINISTRATION: DOSTAX Capsules should be swallowed whole and should not be chewed or crushed, nor should the capsule be opened and its contents sprinkled on food or mixed with liquids. All of these might affect the enteric coating. DOSTAX Capsules should be given without regard to meals.

INDICATION	RECOMMENDED DOSE	MAINTENANCE DOSE	SPECIAL POPULATION
MDD	Acute Treatment: 60 mg/day (once daily or as 30 mg twice daily)	60 mg/day	30 mg once daily for 1 week, to allow patients to adjust to the medication before increasing to 60 mg once daily
GAD	60 mg/day (once daily)	60 mg/day for 10 weeks. Increase in dose beyond 60 mg/day should be in increments of 30 mg once daily	30 mg once daily for 1 week, to allow patients to adjust to the medication before increasing to 60 mg once daily
DPNP	60 mg/day (once daily)	60 mg once daily for 12 weeks	Lower starting dose and gradual increase in dose should be considered for patients with renal impairment
Fibromyalgia	30 mg once daily for 1 week to recommended dose of 60 mg administered once daily	60 mg once daily upto 3 months	

SPECIAL INSTRUCTIONS TO THE PHYSICIAN: Hepatic Insufficiency: Duloxetine should ordinarily not be administered to patients with any hepatic insufficiency. Severe Renal Impairment: Duloxetine is not recommended for patients with end-stage renal disease or severe renal impairment (estimated creatinine clearance <30 mL/min). Elderly Patients: No dose adjustment is recommended for elderly patients on the basis of age. As with any drug, caution should be exercised in treating the elderly. Controlled Narrow-Angle Glaucoma: Duloxetine was associated with an increased risk of mydriasis; therefore, it should be used cautiously in patients with controlled narrow-angle glaucoma. Glycemic Control in Patients with Diabetes: Glycemic control should be carefully monitored in patients with diabetes who are given duloxetine for DPNP. Delayed Gastric Emptying: Caution is advised in using duloxetine in patients with conditions that may slow gastric emptying (e.g., some diabetics). Discontinuing Duloxetine: A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. Switching Patients to or from a Monoamine Oxidase Inhibitor: At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with duloxetine. In addition, at least 5 days should be allowed after stopping duloxetine before starting an MAOI. Overdosage: There is no specific antidote to duloxetine but if serotonin syndrome ensues, specific treatment may be considered (such as cyproheptadine and/or temperature control). In case of acute overdose, treatment should consist of those general measures employed in the management of overdose with any drug.

STORAGE/PRECAUTIONS: Store in a cool, dry and dark place between 15-30 °C. Keep all medicines out of the children' s reach.

PRESENTATION: DOSTAX Capsules 30 & 60 mg are available in packing containing 10 capsules, respectively.

**Scotmann Specs.*

عمومی خوراک: ڈاکٹر کی ہدایت کے مطابق۔

احتیاط: دوا صرف مستند ڈاکٹر کے زیرِ ہدایت استعمال کریں۔ روشنی، نمی اور گرمی سے بچائیں۔ 15 سے 30 ڈگری سینٹی گریڈ کے درمیان محفوظ کریں۔ تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

Complete Medical Information available only for doctors on request.

scotmann PHARMACEUTICALS

Manufactured by: **SCOTMANN PHARMACEUTICALS**

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