ZULOXET Capsules

ذولوکسٹ کیپسولز

(ڈولوکسٹین)

(Duloxetine Delayed Release Capsules USP)

COMPOSITION:
Each capsule contains:
Duloxetine HCl USP enteric coated pellets eq. to Duloxetine ... 20mg, 30mg & 60mg. [USP Specs.]

PHARMACOLOGICAL PROPERTIES: Pharmacodynamics: Preclinical studies have shown that 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). In several preclinical models of neuropathic pain, Duloxetine normalized the pain thresholds and also weakened the pain behavior in a model of persistent pain.

Pharmacokinetics: Duloxetine has an elimination half life of about 12 hours (range 8 to 17 hours) and its pharmacokinetics are dose proportional over the therapeutic range. Steady-state plasma concentrations are typically achieved after 3 days of dosing. Elimination of Duloxetine is mainly through hepatic metabolism involving two P450 isozymes, CYP1A2 and CYP2D6.

Absorption and Distribution: Orally administered Duloxetine Hydrochloride is well absorbed. There is a median 2 hour lag until absorption begins (T_{lag}), 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. Duloxetine is highly bound (>90%) to proteins in human plasma, binding primarily to albumin and α-acid glycoprotein. Plasma protein binding of Duloxetine is not affected by renal or hepatic impairment. Duloxetine is extensively metabolized and metabolites are excreted in the urine.

THERAPEUTIC INDICATIONS: ZULOXET (Duloxetine) is a serotonin and norepinephrine reuptake inhibitor (SNRI), indicated for:
Major Depressive Disorder: ZULOXET (Duloxetine) is indicated for the treatment of major depressive disorder (MDD). The efficacy of **ZULOXET** (Duloxetine) was established in four short term and one maintenance trial in adults.
Generalized Anxiety Disorder: ZULOXET (Duloxetine) is indicated for the treatment of generalized anxiety disorder (GAD). The efficacy of **ZULOXET** (Duloxetine) was established in three short term trials and one maintenance trial in adults.
Diabetic Peripheral Neuropathic Pain: ZULOXET (Duloxetine) is indicated for the management of neuropathic pain (DPNP) associated with diabetic peripheral neuropathy.
Fibromyalgia: ZULOXET (Duloxetine) is indicated for the management of fibromyalgia (FM).

Chronic Musculoskeletal Pain: ZULOXET (Duloxetine) is indicated for the management of chronic musculoskeletal pain. This has been established in studies in patients with chronic low back pain (CLBP) and chronic pain due to osteoarthritis.

CONTRA-INDICATIONS: Hypersensitivity to the active substance, or to any of its excipients. Use of non-selective, irreversible Monoamine Oxidase Inhibitors (MAOIs) with Duloxetine is contra-indicated. Duloxetine is not to be used with fluvoxamine, ciprofloxacin or enoxacine since these cause elevated plasma concentrations of Duloxetine. Severe renal impairment (creatinine clearance <30ml/min).

DOSAGE AND ADMINISTRATION: ZULOXET (Duloxetine) should generally be administered once daily without regard to meals. **ZULOXET** (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.

Indications	Starting Dose	Target Dose	Maximum Dose
Major Depressive Disorder (MDD)	40mg/day to 60mg/day	Acute Treatment: 40mg/day (20mg twice daily) to 60mg/day (once daily or as 30mg twice daily); Maintenance Treatment: 60mg/day	120mg/day
Generalized Anxiety Disorder (GAD)	60mg/day	60mg/day (once daily) OR 30mg twice daily	120mg/day
Diabetic Peripheral Neuropathic Pain (DPNP)	60mg/day	60mg/day (once daily) OR 30mg twice daily	60mg/day
Fibromyalgia (FM)	30mg/day	60mg/day (once daily) OR 30mg twice daily	60mg/day
Chronic Musculoskeletal Pain	30mg/day	60mg/day (once daily) OR 30mg twice daily	60mg/day

Some patients may benefit from starting at 30mg once daily. There is no evidence that doses greater than 60mg/day confers additional benefit, while some adverse reactions were observed to be dose-dependent.
Discontinuation of treatment: Abrupt discontinuation of the treatment should be avoided. When stopping treatment with Duloxetine, the dose has to be gradually reduced over a period of one to two weeks in order to reduce the risk of withdrawal reactions.

DOSING IN SPECIAL POPULATIONS: Hepatic Insufficiency: It is recommended that **ZULOXET** (Duloxetine) should ordinarily not be administered to patients with any hepatic insufficiency.

Severe Renal Impairment: ZULOXET (Duloxetine) is not recommended for patients with end stage renal disease or severe renal impairment (estimated creatinine clearance <30 ml/min).

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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.

OVERDOSAGE: Signs and symptoms of overdose includes serotonin syndrome, somnolence, vomiting and seizures. No cases of fatal incidences have been reported. If serotonin syndrome occurs, treatment with cyproheptadine may be considered.

SPECIAL WARNINGS AND PRECAUTIONS: Mania and seizures: Duloxetine to be used with caution in patients of mania or diagnosed for bipolar disorders and/or seizures.

Mydriasis: Mydriasis has been reported with Duloxetine, so to be used with caution in patients with increased intraocular pressure or those who are at a risk of developing acute narrow-angle glaucoma.

Blood pressure and heart rate: Duloxetine is known to increase blood pressure in some patients which is due to noradrenergic effects of Duloxetine. Blood pressure monitoring is recommended in patients with hypertension and cardiac disease at the start of the treatment.

Renal impairment: ZULOXET (Duloxetine) is not recommended for patients with end stage renal disease (requiring dialysis) or severe renal impairment (estimated creatinine clearance [CrCl] <30ml/min). Population PK analysis suggested that mild to moderate degrees of renal dysfunction (estimated CrCl 30-80ml/min) have no significant effect on **ZULOXET** (Duloxetine) apparent clearance.
Use with anti-depressants: Caution to be taken when using Duloxetine in combination with anti-depressants.

Suicide: Major depressive episodes: Cases of suicidal ideation and suicidal behaviors have been reported during the Duloxetine therapy. Close monitoring of the high risk patients should accompany the drug therapy.

USE IN CHILDREN AND ADOLESCENTS: No clinical trials have been carried out with Duloxetine in pediatric population. Duloxetine not to be used in the treatment of children and adolescents under the age of 18.

Hemorrhage: There have been reports of bleeding abnormalities such as purpura, ecchymosis and GI hemorrhages with SSRIs (selective serotonin reuptake inhibitors) and SNRIs (serotonin/nor epinephrine reuptake inhibitors). Caution to be taken in patients on anti-coagulant therapies.

Hyponatremia: Has been reported rarely in elderly with Duloxetine. Caution required in patients at increased risk of hyponatremia.

Hepatitis/Liver Enzymes: Cases of liver injury, increase in liver enzymes (>10 times the upper limit of normal), hepatitis and jaundice have been reported with Duloxetine. Duloxetine to be used with caution in patients treated with other drugs associated with hepatic injury.

CNS drugs: Caution to be taken when Duloxetine is given in combination with centrally acting medicines and substances like alcohol and sedatives including, benzodiazepines, morphinomimetics, anti-psychotics, phenobarbital, sedative anti-histamines.

Mono Amine Oxidase Inhibitors (MAOIs): Due to the risk of serotonin syndrome, Duloxetine should not be used in combination with non-selective, irreversible Monoamine Oxidase Inhibitors or within two weeks of discontinuing treatment with an MAOI. Keeping in mind the half life of Duloxetine, atleast 5 days should be allowed after stopping Duloxetine before starting an MAOI. Concomitant use of Duloxetine with selective, reversible MAOIs is not recommended.

Serotonin Syndrome: Serotonin syndrome has been reported in patients using SSRIs (paroxetine, fluoxetine) along with serotonergic anti-depressants like SSRIs, tricyclics like clomipramine or amitriptyline, venlafaxine or triptans, tramadol, pethidine and tryptophan.

Drugs Metabolized by CYP2D6: Caution to be taken if Duloxetine is given with medicines which are metabolized by CYP2D6 and have a narrow therapeutic index.

Effect of Other Drugs on Duloxetine: Inhibitors of CYP1A2: Use of Duloxetine with potent inhibitors of CYP1A2 is not recommended.
Warfarin and INR: Administration with Duloxetine along with warfarin shows increase in INR.

PREGNANCY AND LACTATION: Pregnancy: No significant data is available on the use of Duloxetine in pregnancy. Duloxetine is only to be used in pregnancy if benefit justifies the risk to the fetus.

Breast feeding: Duloxetine is excreted in the milk of lactating women. Since there is no safety data of Duloxetine in infants, therefore use of Duloxetine in breast feeding is not advised.

EFFECTS WHILE DRIVING AND HANDLING EQUIPMENTS: Duloxetine does not impair cognitive functions, memory or psychomotor performance. It may however, be associated with sedation or dizziness. Caution to be taken while driving or handling heavy machinery.

UNTOWARD EFFECTS: Patients being treated with Duloxetine for depression, reported most commonly with adverse effects like nausea, dry mouth, headache and constipation. Mild to moderate side effects were seen early during the therapy and subsided as the therapy progressed on. The untoward effects seen in patients with diabetic neuropathic pain were nausea, headache, dizziness and somnolence. In patients with diabetic neuropathic pain, it was seen during the clinical trials that Duloxetine had an elevation in fasting blood glucose levels. However, HbA1c was stable in both placebo and Duloxetine treated groups.

INSTRUCTIONS: Store below 30°C. Protect from heat, light and moisture. Keep out of the reach of children.

PRESENTATION: ZULOXET Capsules 20mg is available in blister pack of 14's. **ZULOXET Capsules 30mg & 60mg** are available in blister pack of 10's.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔ گرمی، روشنی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

PHARMA
Manufactured by:
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