Composition

Diliner ® DR Capsule: Each capsule contains delayed release pellets of Duloxetine HCI equivalent to Duloxetine INN 60 mg.

Pharmacology

Although the exact mechanisms of the antidepressant and central pain inhibitory action of Duloxetine in humans are unknown, the antidepressant and pain inhibitory actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS. 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). Duloxetine undergoes extensive metabolism, but the major circulating metabolites have not been shown to contribute significantly to the pharmacologic activity of Duloxetine.

Indication

Diliner ® (Duloxetine hydrochloride) is indicated for the treatment of

- Depression
- Diabetic Peripheral Neuropathic Pain

Dosage and Administration

Initial Treatment

Major Depressive Disorder

Duloxetine should be administered at a total dose of 40 mg/day (given as 20 mg BID) to 60 mg/day (given either once a day or as 30 mg BID) without regard to meals. There is no evidence that doses greater than 60 mg/day confer any additional benefits.

Diabetic Peripheral Neuropathic Pain

Duloxetine should be administered at a total dose of 60 mg/day given once a day, without regard to meals.

While a 120 mg/day dose was shown to be safe and effective, there is no evidence that doses higher than 60 mg confer additional significant benefit, and the higher dose 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, a lower starting dose and gradual increase in dose should be considered for patients with renal impairment.

Maintenance/Continuation/Extended Treatment

Major Depressive Disorder

It is generally agreed that acute episodes of major depression require several months or longer of sustained pharmacologic therapy. There is insufficient evidence available to answer the question of how long a patient should continue to be treated with Duloxetine. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

Diabetic Peripheral Neuropathic Pain

As the progression of diabetic peripheral neuropathy is highly variable and management of pain is empirical, the effectiveness of Duloxetine must be assessed individually. Efficacy beyond 12 weeks has not been systematically studied in placebo-controlled trials, but a one-year open-label safety study was conducted.

Contraindication and Precaution

Known hypersensitivity to Duloxetine.

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated.

In clinical trials, Duloxetine use was associated with an increased risk of mydriasis; therefore, its use should be avoided in patients with uncontrolled narrow-angle glaucoma.

Side Effect

The most commonly observed adverse events in Duloxetine-treated MDD patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were: nausea; dry mouth; constipation; decreased appetite; fatigue; somnolence; and increased sweating.

The most commonly observed adverse events in Duloxetine-treated DPN patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were: nausea; somnolence; dizziness; constipation; dry mouth; decreased appetite; and asthenia.

Precaution & Warning

Hepatotoxicity - Duloxetine increases the risk of elevation of serum transaminase levels. Because it is possible that Duloxetine and alcohol may interact to cause liver injury, Duloxetine should ordinarily not be prescribed to patients with substantial alcohol use.

Effect on Blood Pressure -Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment.

Activation of Mania/Hypomania - Duloxetine should be used cautiously in patients with a history of mania.

Seizures - Duloxetine should be prescribed with care in patients with a history of a seizure disorder.

Controlled Narrow-Angle Glaucoma- In clinical trials, Duloxetine was associated with an increased risk of mydriasis; therefore, it should be used cautiously in patients with controlled narrow-angle glaucoma.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

Because Duloxetine is an inhibitor of both serotonin and norepinephrine reuptake, it is recommended that Duloxetine not be used in combination with an MAOI, 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.

Drug Interaction

Potential for Other Drugs to Affect Duloxetine

Both CYP1A2 and CYP2D6 are responsible for Duloxetine metabolism.

Inhibitors of CYP1A2 - Concomitant use of duloxetine with fluvoxamine, an inhibitor of CYP1A2, results in approximately a 6-fold increase in AUC and about a 2.5-fold increase in Cmax of duloxetine. Some quinolone antibiotics would be expected to have similar effects and these combinations should be avoided.

Inhibitors of CYP2D6 - Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 may result in higher concentrations of duloxetine. Similar effects would be expected with other potent CYP2D6 inhibitors (e.g., Paroxetine, fluoxetine, quinidine).

Potential for Duloxetine to Affect Other Drugs
Duloxetine does not induce CYP1A2 activity, and it is unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates.

Duloxetine is a moderate inhibitor of CYP2D6. Co-administration of Duloxetine with other drugs that are extensively metabolized by this isozyme and which have a narrow therapeutic index, including certain antidepressants (tricyclic antidepressants [TCAs]), phenothiazines and Type 1C antiarrhythmics (e.g., propafenone, flecainide), should be approached with caution. Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, Duloxetine and thioridazine should not be co-administered.

Duloxetine may have a clinically important interaction with alcohol & other CNS acting drugs. 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.

Storage Condition
Store in a cool and dry place, protected from light and moisture.

How Supplied
Diliner ® DR Capsule: Each box contains 3 x 6's Delayed Release Capsule in alu-alu blister packing.