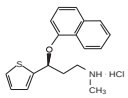
04-03-2019

Dultix™ DR Capsules

(Duloxetine HCl)

DESCRIPTION:

Dultix™ DR is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) for oral administration. Its chemical designation is (+)-(S)-N-methyl-•-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride. The empirical formula is $C_{18}H_{19}NOS•HCl$,. The structural formula is:



COMPOSITION:

Dultix™ DR 20mg Capsules
Each capsule contains:
Duloxetine HCl delayed release pellets MS
equivalent to Duloxetine USP 20mg

Dultix™ DR 40mg Capsules
Each capsule contains:
Duloxetine HCl delayed release pellets MS
equivalent to Duloxetine USP 40mg

Dultix™ DR 30mg Capsules
Each capsule contains:
Duloxetine HCl delayed release pellets MS
equivalent to Duloxetine USP 30mg

Dultix™ DR 60mg Capsules
Each capsule contains:
Duloxetine HCl delayed release pellets MS
equivalent to Duloxetine USP 60mg

CLINICAL PHARMACOLOGY:

Mechanism of Action

Duloxetine is a selective serotonin and noradrenaline reuptake inhibitor, and weakly inhibits dopamine uptake with no significant affinity for histaminergic, dopaminergic, cholinergic and adrenergic receptors

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:

Absorption

Orally administered duloxetine hydrochloride is well absorbed. 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 hours delay in absorption and a one-third increase in apparent clearance of duloxetine after an evening dose as compared to a morning dose. The absolute oral bioavailability of duloxetine ranges from 32% to 80% (mean of 50%)

Distribution

Duloxetine is highly bound (>90%) to proteins in human plasma, binding primarily to albumin and •1-acid glycoprotein. Plasma protein binding of duloxetine is not affected by renal or hepatic impairment

Metabolism

Duloxetine undergoes extensive metabolism. The 2 major metabolites found in plasma and urine are the glucuronide conjugate of 4-hydroxy duloxetine, and the sulfate conjugate of 5-hydroxy, 6-methoxy duloxetine. Both CYP2D6 and CYP1A2 catalyze the formation of the initial oxidation steps to form 4-, 5- and 6-hydroxy duloxetine. The metabolites circulating in plasma are in the conjugated form and are not pharmacologically active

Elimination

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

THERAPEUTIC INDICATIONS:

Dultix™ DR is a serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for:

- Major Depressive Disorder (MDD)
- Generalized Anxiety Disorder (GAD)
- Diabetic Peripheral Neuropathic Pain (DPNP)
- Fibromyalgia (FM)
- Chronic Musculoskeletal Pain

DOSAGE AND METHOD OF ADMINISTRATION:

Take **Dultix™ DR** once daily, with or without food. Swallow **Dultix™ DR** whole; do not crush or chew, do not open capsule. Take a missed dose as soon as it is remembered. Do not take two doses of **Dultix™ DR** at the same time

Indication	Starting Dose	Target Dose	Maximum Dose
Major Depressive Disorder	40mg/day to 60mg/day	Acute Treatment: 40mg/day (20mg twice daily) to 60mg/day (once daily or 30mg twice daily); Maintenance Treatment: 60mg/day	120mg/day
Generalized Anxiety Disorder			
Adults	60mg/day	60mg/day (once daily)	120mg/day
Elderly	30mg/day	60mg/day (once daily)	120mg/day
Children and Adolescents (7 to 17 years of age)	30mg/day	30 to 60mg/day (once daily)	120mg/day
Diabetic Peripheral Neuropathic pain	60mg/day	60mg/day (once daily)	60mg/day
Fibromyalgia	30mg/day	60mg/day (once daily)	60mg/day
Chronic Musculoskeletal pain	30mg/day	60mg/day (once daily)	60mg/day

OR
As directed by the physician

Dosing considerations

- 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
- To discontine **Dultix™ DR**, gradually reduce dosage to avoid discontinuation symptoms

210mm

120mm

USE IN SPECIFIC POPULATIONS:
Gender: Duloxetine's half-life is similar in men and women. Dosage adjustment based on gender is not necessary
Smoking Status: Duloxetine bioavailability (AUC) appears to be reduced by about one-third in smokers. Dosage modifications are not recommended for smokers
Hepatic Impairment: Avoid use in patients with chronic liver disease or cirrhosis
Severe Renal Impairment: Avoid use in patients with severe renal impairment, GFR <30 mL/min
Glycemic Control in Patients with Diabetes: As observed in DPNP trials, duloxetine treatment worsens glycemic control in some patients with diabetes
Pregnancy: Pregnancy Category C: There are no adequate and well-controlled studies of duloxetine administration in pregnant women
Nursing Mothers: Duloxetine is present in human milk. At steady state, the concentration of duloxetine in breast milk was approximately 25% that of maternal plasma
Geriatric Use: In an analysis of data from all placebo-controlled-trials, patients treated with duloxetine, reported a higher rate of falls compared to patients treated with placebo

CONTRAINDICATIONS:
- Hypersensitivity to the active substance or to any of its excipients
- Monoamine Oxidase Inhibitors (MAOIs) — 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 also 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
- Duloxetine should not be used in combination with fluvoxamine, ciprofloxacin or enoxacin (i.e. potent CYP1A2 inhibitors), since the combination results in elevated plasma concentration of duloxetine

WARNINGS AND PRECAUTIONS:

SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber

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

Mydriasis: Mydriasis has been reported in association with duloxetine, therefore, caution should be used when prescribing duloxetine to 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

Renal impairment: Increased plasma concentrations of duloxetine occur in patients with severe renal impairment on haemodialysis (creatinine clearance <30ml/min)

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

St. John's Wort: Adverse reactions may be more common during concomitant use of duloxetine and herbal preparations containing St. John's Wort

Suicide: Major Depressive Disorder and Generalised Anxiety Disorder: Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs

Diabetic Peripheral Neuropathic Pain: As with other medicinal products with similar pharmacological action (antidepressants), isolated cases of suicidal ideation 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 at any time

Use in children and adolescents under 18 years of age:
The safety and effectiveness in pediatric patients less than 7 years of age have not been established. Use of duloxetine in a child or adolescent must balance the potential risks with the clinical need

Haemorrhage:
There have been reports of bleeding abnormalities, such as ecchymoses, purpura and gastrointestinal haemorrhage with selective serotonin reuptake inhibitors (SSRIs) and serotonin/noradrenaline reuptake inhibitors (SNRIs), including duloxetine. Caution is advised in patients taking anticoagulants

Hyponatraemia:
Hyponatraemia has been reported when administering duloxetine, including cases with serum sodium lower than 110 mmol/l.

Hepatitis/increased liver enzymes: Duloxetine should be used with caution in patients treated with other medicinal products associated with hepatic injury

DRUG INTERACTIONS:
Monoamine oxidase inhibitors (MAOIs): Due to the risk of serotonin syndrome, duloxetine should not be used in combination with non-selective irreversible monoamine oxidase inhibitors (MAOIs), or within at least 14 days of discontinuing treatment with an MAOI

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, sedative antihistamines)

Serotonin syndrome: 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, MAOIs 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 metabolised by CYP1A2: The pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by co-administration with duloxetine (60 mg twice daily)

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

OVERDOSAGE:
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

STABILITY:
See expiry on the pack

PRESENTATION:
Dultix™ DR 20mg capsules in a pack of 14's
Dultix™ DR 30mg capsules in a pack of 14's
Dultix™ DR 40mg capsules in a pack of 10's
Dultix™ DR 60mg capsules in a pack of 10's

INSTRUCTIONS:
Keep out of reach of children
Avoid exposure to heat, light and humidity
Store between 15 to 30°C
Improper storage may deteriorate the medicine

ڈلٹکس™ ڈی آر کیپسول

(ڈیولوکسٹین ہائیڈروکلورائیڈ)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں

بچوں کی پہنچ سے دور رکھیں

دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com

R.N-01/HA/03/19

210mm

120mm