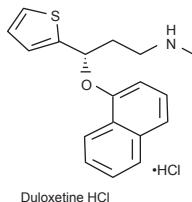


Lyta™ 40

(Duloxetine)

Capsules 40mg

Lyta 40 (Duloxetine) is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI). Its chemical formula is (+)-(S)-N-Methyl-β-(1-naphthoxy)-2-thiophenepropylamine hydrochloride and molecular formula is C₁₈H₁₉NOS•HCl. The structural formula is as:



Duloxetine HCl

QUALITATIVE AND QUANTITATIVE COMPOSITION

Lyta 40 (Duloxetine) is available for oral administration as:

Lyta 40 Capsules 40mg

Each capsule contains:

Enteric coated pellets of Duloxetine Hydrochloride equivalent to Duloxetine...40mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Duloxetine is a combined serotonin (5-HT) and noradrenaline (NA) reuptake inhibitor. It weakly inhibits dopamine reuptake, with no significant affinity for histaminergic, dopaminergic, cholinergic and adrenergic receptors.

PHARMACOKINETICS

Absorption

Orally administered duloxetine hydrochloride is well absorbed. Maximal plasma concentrations (C_{max}) of duloxetine occurs within 6 hours post dose. Food does not affect the maximal plasma concentrations (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 11%. The absolute oral bioavailability of duloxetine ranged from 32% to 80% (mean of 50%).

Distribution

Duloxetine is approximately 96% bound to human plasma proteins. Duloxetine binds to both albumin and α1-acid glycoprotein. Protein binding is not affected by renal or hepatic insufficiency.

Metabolism

Duloxetine is extensively metabolized. Both cytochromes P450-2D6 and 1A2 catalyze the formation of the two major metabolites, glucuronide conjugate of 4-hydroxy duloxetine and sulphate conjugate of 5-hydroxy, 6-methoxy duloxetine. The circulating metabolites of duloxetine are considered as pharmacologically inactive.

Excretion

The elimination half-life (t_{1/2}) of duloxetine ranges from 8 to 17 hours (mean of 12 hours). After an oral dose the apparent plasma clearance of duloxetine ranges from 33L/hr to 261L/hr (mean 101L/hr). These metabolites are principally excreted in the urine; about 20% is excreted in the feces. Less than 1% of a dose is excreted in the urine as unchanged duloxetine.

Special Populations

Gender

There are differences of pharmacokinetics like in males & females (apparent plasma clearance is approximately 50% lower in females). Gender-based pharmacokinetic differences do not justify the recommendation for using a lower dose for female patients.

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Age

Differences in pharmacokinetics between younger and elderly females (>65 years) (AUC increases by about 25% and half-life (t_{1/2}) is about 25% longer in the elderly), although the magnitude of these changes is not sufficient to justify adjustments to the dose. As a general recommendation, caution should be exercised when treating the elderly.

Renal Impairment

End stage renal disease (ESRD) patients receiving dialysis have 2-fold higher duloxetine maximal plasma concentrations (C_{max}) and AUC values.

Hepatic Impairment

Moderate liver disease affects the pharmacokinetics of duloxetine. The apparent plasma clearance of duloxetine becomes 79% lower, the apparent terminal half-life (t_{1/2}) 2.3-times longer, and the AUC 3.7-times higher in patients with moderate liver disease.

THERAPEUTIC INDICATIONS

Lyta 40 (Duloxetine) is indicated for women for the treatment of moderate to severe stress urinary incontinence (SUI).

DOSAGE AND ADMINISTRATION

Lyta 40 (Duloxetine) 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. Lyta 40 (Duloxetine) should be given without regard to meals.

The recommended dose is 40mg twice daily. After 24 weeks of treatment, patients should be reassessed in order to evaluate the benefit and tolerability of the therapy. Some patients may benefit from starting treatment at a dose of 20mg twice daily for two weeks before increasing to the recommended dose of 40mg twice daily. Dose escalation may decrease, though not eliminate, the risk of nausea and dizziness.

Special Population

Renal Impairment

No dosage adjustment is necessary for patients with mild or moderate renal dysfunction creatinine clearance (CLcr 30mL/min to 80mL/min).

Discontinuation of Treatment

Abrupt discontinuation should be avoided. When stopping treatment with Lyta 40 (Duloxetine) the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions. 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.

CONTRAINDICATIONS:

Duloxetine is contraindicated in patients:

- taking monoamine oxidase inhibitors (MAOIs), due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs.
- with hypersensitivity to the active substance or to any of the excipients.
- taking with fluvoxamine, ciprofloxacin or enoxacin (i.e., potent CYP1A2 inhibitors).
- with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis.
- with severe renal insufficiency with creatinine clearance (CLcr) < 30mL/min.
- with liver disease resulting in hepatic insufficiency.

ADVERSE REACTIONS

Very Common

Nausea, headache, insomnia, fatigue, somnolence, dry mouth, dizziness and constipation.

Common

Anorexia, diarrhea, dyspepsia, vomiting, anxiety, visual disturbances, tremor, weight gain or loss, sexual dysfunction, nervousness, lethargy, yawning, hot flushes, increased sweating and pruritus. Dose-related increase in blood pressure also occurs in some patients.

Rare

Reversible increases in liver enzymes, tachycardia, ecchymosis, urinary hesitation, skin rashes, photosensitivity reactions, hepatitis, cholestatic jaundice, convulsions and activation of mania or hypomania. Orthostatic hypotension and syncope, serotonin syndrome, and akathisia, suicidal ideation, hyponatremia, possibly due to inappropriate secretion of antidiuretic hormone, associated with the use of antidepressants, particularly in the elderly.

WARNING AND PRECAUTIONS

Suicidal thoughts/behaviours

Suicidal thoughts and suicidal behaviours can occur during duloxetine therapy or early after treatment discontinuation. Close supervision of patients, and in particular those at high risk, should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts, and unusual changes in behaviour, and to seek medical advice immediately if these symptoms present.

Severe Skin Reactions

Duloxetine can cause severe skin reactions, including erythema multiforme and Stevens-Johnson Syndrome (SJS). 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.

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

Caution should be used when prescribing duloxetine to patients with increased intra-ocular pressure or those at risk of acute narrow angle glaucoma.

Blood Pressure and Heart Rate

Duloxetine is associated with an increase in blood pressure and clinically significant hypertension in some patients. Therefore, in patients with known hypertension and/or other cardiac diseases, blood pressure monitoring is recommended, especially during the first month of treatment. Duloxetine should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure. Caution should also be exercised when duloxetine is used with medicinal products that may impair its metabolism. For patients who experience a sustained increase in blood pressure while receiving duloxetine, either dose reduction or gradual discontinuation should be considered. In patients with uncontrolled hypertension, duloxetine should not be initiated.

Use with Antidepressants

Caution should be exercised when using duloxetine in combination with antidepressants.

Hemorrhage

Bleeding abnormalities, such as ecchymoses, purpura and gastrointestinal hemorrhage, with selective serotonin reuptake inhibitors (SSRIs) and serotonin/noradrenaline reuptake inhibitors (SNRIs). Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function and in patients with known bleeding tendencies.

Akathisia/Psychomotor Restlessness

The use of duloxetine is associated with the development of

akathisia, characterized by a subjectively unpleasant or distressing restlessness and need to move, often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Hepatitis/Increased Liver Enzymes

Severe elevations of liver enzymes (>10 times upper limit of normal), hepatitis and jaundice may occur with duloxetine. Most of them occur during the first month of treatment. The pattern of liver damage was predominantly hepatocellular. Duloxetine should be used with caution in patients treated with other medicinal products associated with hepatic injury.

Hyponatremia

Caution is required in patients at increased risk for hyponatremia, such as elderly, cirrhotic or dehydrated patients or patients treated with diuretics. Hyponatremia may be due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

Pregnancy

There are no adequate data on the use of duloxetine in pregnant women. Duloxetine should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

The safety of duloxetine in infants is not known and the use of duloxetine while breast-feeding is not recommended.

OVERDOSAGE

Fatal outcomes have been reported for acute overdoses, primarily with mixed overdoses, but also with duloxetine only, at doses as low as 1000mg. Signs and symptoms of overdose (duloxetine alone or with mixed drugs) include somnolence, coma, serotonin syndrome, seizures, syncope, tachycardia, hypotension, hypertension and vomiting.

There is no specific antidote to duloxetine. In the treatment of overdose, oral activated charcoal should be considered if more than 7.5mg/kg of duloxetine has been ingested and the patient presents within 1 hour of ingestion; this should be followed by symptomatic and supportive therapy. Dialysis, hemoperfusion, exchange perfusion and measures to increase urine production are considered unlikely to be of benefit.

HOW SUPPLIED

Lyta 40 (Duloxetine) Capsules 40mg are available in blister pack of 14's.

STORAGE

Store at 25°C (Excursions permitted between 15°C to 30°C). Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:



29-30/27,
K.I.A., Karachi,
Pakistan

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