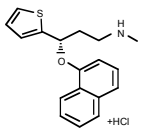
Lyta™

(Duloxetine)

لايتا

Capsules 20mg, 30mg, 60mg

Lyta (Duloxetine) is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI). Its chemical formula is (+)-(S)-N-Methyl-β-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride and molecular formula is $C_{18}H_{19}NOS$•HCl. The structural formula is as:



Duloxetine HCl

QUALITATIVE AND QUANTITATIVE COMPOSITION

Lyta (Duloxetine) is available for oral administration as:

1. Lyta Capsules 20mg
   Each capsule contains:
   Enteric coated pellets of Duloxetine Hydrochloride equivalent to Duloxetine…20mg

2. Lyta Capsules 30mg
   Each capsule contains:
   Enteric coated pellets of Duloxetine Hydrochloride equivalent to Duloxetine…30mg

3. Lyta Capsules 60mg
   Each capsule contains:
   Enteric coated pellets of Duloxetine Hydrochloride equivalent to Duloxetine…60mg

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. Duloxetine dose-dependently increases extracellular levels of serotonin and noradrenaline in various brain areas of animals.

Duloxetine normalizes pain thresholds of neuropathic and inflammatory pain and attenuated pain behaviour in a model of persistent pain. The pain inhibitory action of duloxetine is believed to be a result of potentiation of descending inhibitory pain pathways within the central nervous system.

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 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 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 α_1-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.

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 (Duloxetine) is indicated:

- for the treatment of major depressive disorder (MDD).
- for the management of neuropathic pain (DPNP) associated with diabetic peripheral neuropathy.
- for the treatment of generalized anxiety disorder.
- for the management of fibromyalgia.
- for the treatment of moderate to severe stress urinary incontinence in women.

DOSAGE AND ADMINISTRATION

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

Major Depressive Disorder

Usual initial doses of 20mg or 30mg twice daily, or 60mg once daily. A lower starting dose of 30mg once daily for the first week may be suitable for some patients, to allow them to adjust to the effects of duloxetine before increasing the dose. A dose of 60mg once daily may be used for maintenance therapy.

Generalised Anxiety Disorder

The recommended starting dose in patients with generalised anxiety disorder is 30mg once daily. In patients with insufficient response, the dose should be increased to 60mg. In patients with insufficient response to 60mg, escalation up to 90mg or 120mg may therefore be considered. Dose escalation should be based upon clinical response and tolerability.

Diabetic Peripheral Neuropathic Pain

The usual dose is 60mg once daily. Some patients who respond insufficiently to this dose may benefit from up to 120mg daily in divided doses. Response to therapy should be evaluated after 2 months and every 3 months thereafter.

Fibromyalgia

The recommended dose for Lyta (Duloxetine) is 60mg administered once daily. Treatment should begin at 30mg once daily for 1 week, to allow patients to adjust to the medication before increasing to 60mg once daily. Some patients may respond to the starting dose.

Stress urinary incontinence

Usual initial doses are 40mg twice daily; however, some patients may benefit from an initial dose of 20mg twice daily for 2 weeks before increasing to 40mg twice daily.

Special Population

Renal Impairment

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

Discontinuation of Treatment

Abrupt discontinuation should be avoided. When stopping treatment with Lyta (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 enoxacine (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 (CL_{CR}) < 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 increases 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, hyponatraemia, 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 disease, 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.

Elderly
Caution should be exercised when treating the elderly with the maximum dosage.

Akathisia/Psychomotor Restlessness
The use of duloxetine is associated with the development of akathisia, characterised 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 months 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, 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 overdosage, 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 (Duloxetine) Capsules 20mg are available in blister packs of 14's.
Lyta (Duloxetine) Capsules 30mg are available in blister packs of 10's.
Lyta (Duloxetine) Capsules 60mg are available in blister packs of 10'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.

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Getz pharma (PVT) LIMITED
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