Felice
(Duloxetine) USP

CAPSULES
20, 30 & 60mg

DESCRIPTION:
Duloxetine Hydrochloride is the hydrochloride salt of duloxetine, a fluoxetine derivative belonging to the class of selective serotonin (5-HT) and norepinephrine (NE) reuptake inhibitors (SSNRIs) and exhibiting antidepressant activity. Duloxetine chemical formula is (+)-(S)-N-Methyl-B-(1-naphthyloxy)-2-thiphenepropylamine hydrochloride and molecular formula is C18H19NOS.HCl.

COMPOSITION
Felice 20mg Capsules: Each capsule contains:
Duloxetine as hydrochloride (enteric coated pellets 17.0%) USP.....20mg
Felice 30mg Capsules: Each capsule contains:
Duloxetine as hydrochloride (enteric coated pellets 17.0%) USP.....30mg
Felice 60mg Capsules: Each capsule contains:
Duloxetine as hydrochloride (enteric coated pellets 17.0%) USP.....60mg

CLINICAL PHARMACOLOGY
Mechanism of Action:
Duloxetine selectively prevents the reuptake of serotonin (5-HT) and norepinephrine (NE) via transporter complexes on the pre-synaptic membrane, thereby increasing the level of these neurotransmitters within the synaptic cleft. As a result, this agent potentiates serotonergic and noradrenergic activities in the central nervous system, and alleviates depression and neuropathy sensations, such as pain and tingling.

Duloxetine is a combined serotonin and norepinephrine 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 attenuates pain behavior in a model of persistent pain. The pain inhibitory action of duloxetine is accepted to be the result of potentiation of descending inhibitory pain pathways within the central nervous system.

PHARMACOKINETICS
Absorption
Duloxetine is well absorbed after oral administration. Maximal plasma concentrations (Cmax) of duloxetine occurs within 6 hours after dose. Food delays the time to reach peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption 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 alpha-1 acid glycoprotein. Protein binding is not affected by renal or hepatic insufficiency.
Metabolism
Duloxetine is extensively metabolized and its metabolites are mainly excreted in urine. Cytochromes P450- 2D6 and 1A2 catalyze the formation of two metabolites, glucuronide conjugate of 4-hydroxy duloxetine and sulphate conjugate of 5-hydroxy, 6-methoxy duloxetine. The circulating metabolites of duloxetine are thought to be pharmacologically inactive.
Elimination
The elimination half-life of duloxetine varies 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, with a mean 101L/hr.
Route of Excretion
About 70% of duloxetine is excreted in the urine mainly as conjugated metabolites. Another 20% is present in the feces as the parent drug, 4-hydroxy metabolite, and an uncharacterized metabolite. Biliary secretion is thought to play a role due to timeline of fecal excretion exceeding the time expected of normal GI transit.
Special Populations
Gender
There are pharmacokinetics differences in males & females (apparent plasma clearance is approximately 50% lower in females). These gender-based pharmacokinetic differences do not justify the recommendation for using a lower dose for female patients.
Age
There are pharmacokinetic differences between younger and elderly females (>65 years) (AUC increases by about 25% and half-life (t1/2) is about 25% longer in the elderly), although the magnitude of these changes is not significant to justify adjustments of the dose. As a general recommendation, caution should be taken when treating the elderly.
Renal Impairment
In patients of end stage renal disease (ESRD) receiving dialysis, there is 2-fold higher duloxetine maximal plasma concentration (Cmax) and AUC values. No dosage adjustment is necessary for patients with mild of moderate renal dysfunction (creatinine clearance CLcr 30mL/min to 80mL/min).
Hepatic Impairment
Moderate liver disease alters the pharmacokinetics of Duloxetine. The apparent plasma clearance of duloxetine becomes 79% lower, the apparent terminal half-life (t1/2) 2.3-times longer and the AUC 3.7-times higher in patients with moderate liver disease.
Breast feeding
Safety of duloxetine in infants is not known, the use of duloxetine while breast-feeding is not recommended.

THERAPEUTICS INDICATIONS AND DOSAGE
Duloxetine is indicated for the:
- Treatment of major depressive disorder (MDD)
- Treatment of generalized anxiety disorder (GAD)
- Treatment of diabetic peripheral neuropathic pain (DPNP)
- Treatment of Fibromyalgia
- Treatment of Chronic Pain

Administration:
Oral: Administer without regard to meals. Capsule should be swallow as whole and should not be crushed or chewed.

Major Depressive Disorder
Initial dose: 20 mg to 30 mg orally 2 times a day
Maintenance dose: 60 mg per day, given either once a day OR 30 mg orally 2 times a day
Maximum dose: 120 mg/day

Generalized Anxiety Disorder
Initial dose: 60 mg orally once a day
Maintenance dose: 60 to 120 mg orally once a day
Maximum dose: 120 mg/day

Diabetic Peripheral Neuropathic Pain
Initial dose: 30 to 60 mg orally once a day
Maintenance dose: 60 mg orally once a day

Fibromyalgia
Initial dose: 30 mg orally once a day for at least 1 week
Maintenance dose: 30 to 60 mg orally once a day

Chronic Pain
Initial dose: 30 to 60 mg orally once a day
Maintenance dose: 60 mg orally once a day

Discontinuation of Treatment
Any abrupt discontinuation of Duloxetine should be avoided. While stopping treatment with Duloxetine the dose should be gradually reduced over a period of time, 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:

- Patients with hypersensitivity to the active substance or to any of the excipients.
- Duloxetine concomitant use with nonselective irreversible monoamine oxidase inhibitors (MAOIs) ·
- Duloxetine combination with fluvoxamine, ciprofloxacin or enoxacin
- Patients with uncontrolled hypertension
- Patients with severe renal impairment with creatinine clearance < 30ml/mi
- Patients with liver disease resulting in hepatic impairment

ADVERSE REATIONS

Very Common

Headache, Somnolence, Nausea and Dry mouth

Common

Insomnia, dizziness, diarrhea, dyspepsia, vomiting, constipation, flatulence, anxiety, visual disturbances, tremor, weight loss, sexual dysfunction, lethargy, yawning, hot flushes, increased sweating and palpitations.

Rare

Anaphylactic reaction, Hypo-thyroidism, Hyper-sensitivity disorder, Dehydration, Hyponatraemia, Interstitial lung disease, Eosinophilic pneumonia, Stomatitis, Haematochezia, Breath odour, Hypertensive crisis, Serotonin syndrome, Convulsion, Psychomotor restlessness, Extra-pyramidal symptoms, Microscopic colitis, Hepatic failure, Jaundice, Stevens-Johnson Syndrome, Angio-neurotic oedema, Trismus, Urine odour abnormal, Menopausal symptoms, Galactorrhoea, Hyperprolactinaemia, Postpartum haemorrhage and increased Blood cholesterol.

WARNING AND PRECAUTIONS

Suicidal thoughts/behaviors

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

Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal thoughts prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicidal behaviour, and should receive careful monitoring during treatment.

Serotonin Syndrome

In serotonin syndrome, a potentially life-threatening condition may occur, while using duloxetine concomitantly with other serotonergic agents (including SSRIs, SNRIs tricyclic antidepressants or triptans). And also with agents that impair metabolism of serotonin such as MAOIs, or with antipsychotics or other dopamine antagonists that may affect the serotonergic neurotransmitter systems.

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 use 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 of 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.

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, 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

In case of liver injury, 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 cation 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.

DRUG OVERDOSE

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 over dosage, monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal may be useful in limiting absorption. Duloxetine has a large volume of distribution and forced diuresis, haemoperfusion, and exchange perfusion are unlikely to be beneficial.

HOW SUPPLIED

Felice (Duloxetine) 20mg Capsules: are available in Alu-Alu pack of 2x7's.
Felice (Duloxetine) 30mg Capsules: are available in Alu-Alu pack of 2x5's.
Felice (Duloxetine) 60mg Capsules: are available in Alu-Alu pack of 2x5's.

STORAGE

Store at 15-30°C. Protect from heat, light and moisture. Keep all medicines out of the reach of children. To be sold on the prescription of a registered medical practitioner only.

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

فیلیس (ڈیولوگزیٹین) یو ایس پی

خوراک: دوا ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: دوا کو **15-30°** سینٹی گریڈ پر رکھیں۔

گرمی، روشنی اور نمی سے محفوظ رکھیں۔ تمام دوائیں بچوں کی پہنچ سے دُور رکھیں۔

Manufactured by:
STANDPHARM PAKISTAN (PVT) LTD
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