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Barcode

hovid Duloxetine Delayed-Release Capsule

VIDULxx-0

DESCRIPTION

hovid Duloxetine Delayed-Release Capsule 30 mg: Size "3" hard gelatin capsules with white cap and white body imprinted with '30 mg' on body in black ink, filled with off-white to pale creamish pellets.

hovid Duloxetine Delayed-Release Capsule 60 mg: Size "1" hard gelatin capsules with blue cap and white body imprinted with '60 mg' on body in black ink, filled with off-white to pale creamish pellets.

COMPOSITION

hovid Duloxetine Delayed-Release Capsule 30 mg: Duloxetine hydrochloride 33.68 mg equivalent to Duloxetine 30 mg

hovid Duloxetine Delayed-Release Capsule 60 mg: Duloxetine hydrochloride 67.36 mg equivalent to Duloxetine 60 mg

Excipients: Hydroxyl propyl methyl cellulose E5, sucrose spheres, sucrose, HPMC acetate succinate, triethyl citrate, talc, titanium dioxide, ammonia solution, titanium dioxide, gelatin and printing ink.

ACTIONS AND PHARMACOLOGY

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.

PHARMACOKINETICS

Absorption: Duloxetine is well absorbed after oral administration, with a C_{max} occurring 6 hours post-dose. The absolute oral bioavailability of Duloxetine ranged from 32% to 80% (mean of 50%). Food delays the time to reach the peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11%). These changes do not have any clinical significance.

Distribution: Duloxetine is approximately 96% bound to human plasma proteins. Duloxetine binds to both albumin and alpha1-acid glycoprotein. Protein binding is not affected by renal or hepatic impairment.

Metabolism: Duloxetine is extensively metabolised and the metabolites are excreted principally in urine. Both cytochromes P450-2D6 and 1A2 catalyse the formation of the two major metabolites, glucuronide conjugate of 4-hydroxy Duloxetine and sulphate conjugate of 5-hydroxy, 6-methoxy Duloxetine. Based upon in vitro studies, the circulating metabolites of Duloxetine are considered pharmacologically inactive. The pharmacokinetics of Duloxetine in patients who are poor metabolisers with respect to CYP2D6 has not been specifically investigated. Limited data suggest that the plasma levels of Duloxetine are higher in these patients.

Elimination: The elimination half-life of Duloxetine ranges from 8 to 17 hours (mean of 12 hours). After an oral dose the apparent plasma clearance of Duloxetine ranges from 33 to 261 l/hr (mean 101 l/hr).

INDICATIONS

- Treatment of major depressive disorder,
- Management of neuropathic pain associated with diabetic peripheral neuropathy in adults
- Treatment of generalized anxiety disorder
- Duloxetine is not indicated for use in children and adolescents below 18 years of age.

CONTRAINDICATIONS

Duloxetine is contraindicated in patients with hypersensitivity to the active substance.

Concomitant use of Duloxetine with non-selective, irreversible monoamine oxidase inhibitors (MAOIs) is contraindicated.

Liver disease resulting in hepatic impairment.

Duloxetine should not be used in combination with fluvoxamine, ciprofloxacin or enoxacin (i.e., potent CYP1A2 inhibitors), since the combination results in elevated plasma concentrations of Duloxetine.

Increased plasma concentrations of Duloxetine occur in patients with severe renal impairment on haemodialysis (creatinine clearance <30 ml/min). Duloxetine must not be used in patients with severe renal impairment (creatinine clearance <30 ml/min).

The initiation of treatment with Duloxetine is contraindicated in patients with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis.

WARNINGS AND PRECAUTIONS

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. Cases of hypertensive crisis have been reported with Duloxetine, especially in patients with pre-existing hypertension. 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.

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.

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).

If concomitant treatment with Duloxetine and other serotonergic agents that may affect the serotonergic and/or dopaminergic neurotransmitter systems is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

St John's wort: Adverse reactions may be more common during concomitant use of Duloxetine and herbal preparations containing St John's Wort *(Hypericum perforatum)*.

Suicide: Cases of suicidal thoughts and suidical behaviours have been reported during duloxetine therapy or early after treatment discontinuation in patients treated for major depressive disorder, diabetic peripheral neuropathic pain, children and adolescents under 18 years. Other psychiatric conditions for which Duloxetine is prescribed can also be associated with an increased risk of suicide-related events. 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. A meta-analysis of placebo- controlled clinical trials of antidepressant medicinal products in psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients, and in particular those at high risk, should accompany medicinal product 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.

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 and/or medicinal products known to affect platelet function (e.g., NSAIDs or acetylsalicylic acid (ASA)), and in patients with known bleeding tendencies.

Hyponatraemia: Hyponatraemia has been reported when administering Duloxetine, including cases with serum sodium lower than 110 mmol/l. Hyponatraemia may be due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

The majority of cases of hyponatraemia were reported in the elderly, especially when coupled with a recent history of, or condition pre-disposing to, altered fluid balance. Caution is required in patients at increased risk for hyponatraemia, such as elderly, cirrhotic, or dehydrated patients, or patients treated with diuretics.

Discontinuation of Treatment: Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt. Adverse events seen on abrupt treatment discontinuation occurred in approximately 45% of patients treated with Duloxetine and 23% of patients taking placebo.

The risk of withdrawal symptoms seen with SSRIs and SNRIs may be dependent on several factors, including the duration and dose of therapy and the rate of dose reduction. Generally, these symptoms are mild to moderate; however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally, these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that Duloxetine should be gradually tapered when discontinuing treatment over a period of no less than 2 weeks, according to the patient's needs.

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

Akathisia/Psychomotor Restlessness:
The use of Duloxetine has been 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.

Medicinal product containing duloxetine:
Concomitant use of other products containing duloxetine should be avoided.

Hepatitis/Increased Liver Enzymes:
Cases of liver injury, including severe elevations of liver enzymes (>10-times upper limit of normal), hepatitis, and jaundice have been reported with Duloxetine. Most of them occurred 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.

Sucrose: Duloxetine contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

Sexual dysfunction:
Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction.

There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRIs

PREGNANCY AND LACTATION

Pregnancy: There are no adequate data on the use of Duloxetine in pregnant women. Studies in animals have shown reproductive toxicity at systemic exposure levels (AUC) of Duloxetine lower than the maximum clinical exposure.

The potential risk for humans is unknown. Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). Although no studies have investigated the association of PPHN to SNRI treatment, this potential risk cannot be ruled out with Duloxetine, taking into account the related mechanism of action (inhibition of the re-uptake of serotonin).

As with other serotonergic medicinal products, discontinuation symptoms may occur in the neonate after maternal Duloxetine use near term. Discontinuation symptoms seen with Duloxetine may include hypotonia, tremor, jitterness, feeding difficulty, respiratory distress and seizures. The majority of cases have occurred either at birth or within a few days of birth.

Duloxetine should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus. Women should be advised to notify their physician if they become pregnant, or intend to become pregnant, during therapy.

Lactation: Duloxetine is very weakly excreted into human milk, based on a study of 6 lactating patients who did not breast-feed their children. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose. As the safety of Duloxetine in infants is not known, the use of Duloxetine while breast-feeding is not recommended.

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DRUG INTERACTIONS

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. Based on the half-life of Duloxetine, at least 5 days should be allowed after stopping Duloxetine before starting an MAOI.

The concomitant use of Duloxetine with selective, reversible MAOIs, like moclobemide, is not recommended. The antibiotic linezolid is a reversible non-selective MAOI and should not be given to patients treated with Duloxetine.

Because CYP1A2 is involved in Duloxetine metabolism, concomitant use of Duloxetine with potent inhibitors of CYP1A2 is likely to result in higher concentrations of Duloxetine. Fluvoxamine (100 mg once daily), a potent inhibitor of CYP1A2, decreased the apparent plasma clearance of Duloxetine by about 77% and increased AUCo-t 6-fold. Therefore, Duloxetine should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine.

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). ***Serotonergic agents:*** In rare cases, serotonin syndrome has been reported in 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 CYP2D6: Duloxetine is a moderate inhibitor of CYP2D6.Caution is advised if Duloxetine is co-administered with medicinal products that are predominantly metabolised by CYP2D6 (desipramine, risperidone, tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), particularly if they have a narrow therapeutic index (such as flecainide, propafenone, and metoprolol).

Anticoagulants and antiplatelet agents: Caution should be exercised when Duloxetine is combined with oral anticoagulants or anti-platelet agents due to a potential increased risk of bleeding attributable to a pharmacodynamic interaction. Furthermore, increases in INR values have been reported when Duloxetine was co-administered to patients treated with warfarin. However, concomitant administration of Duloxetine with warfarin under steady-state conditions, in healthy volunteers, as part of a clinical pharmacology study, did not result in a clinically significant change in INR from baseline or in the pharmacokinetics of R- or S-warfarin.

Effects of Other Medicinal Products on Duloxetine

Inducers of CYP1A2: Population pharmacokinetic analyses have shown that smokers have almost 50% lower plasma concentrations of Duloxetine compared with non-smokers.

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).

Oral contraceptives and other steroidal agents: Results of in vitro studies demonstrate that duloxetine does not induce the catalytic activity of CYP3A.

MAIN SIDE/ ADVERSE EFFECTS

The most commonly reported adverse reactions in patients treated with duloxetine were nausea, headache, dry mouth, somnolence and dizziness. However, the majority of common adverse reactions were mild to moderate; they usually started early in therapy, and most tended to subside even as therapy was continued.

Frequency estimate: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥ 1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

- **Infections and infestations**
  Uncommon: Laryngitis
- **Immune system disorders**
  Rare: Anaphylactic reaction, hypersensitivity disorder
- **Endocrine disorders**
  Rare: Hypothyroidism
- **Metabolism and nutrition disorders**
  Common: decreased appetite
  Uncommon: Hyperglycaemia
  Rare: Dehydration, Hyponatraemia, SIADH
- **Psychiatric disorders**
  Common: Insomnia, agitation, libido decreased, anxiety, orgasm abnormal, abnormal dreams
  Uncommon: Suicidal ideation, sleep disorder, bruxism, disorientation apathy
  Rare: Suicidal behaviour, mania, hallucinations, aggression and anger
- **Nervous system disorders**
  Very common: Headache, somnolence
  Common: Dizziness, lethargy, tremor, paraesthesia
  Uncommon: Myoclonus, akathisia, nervousness, disturbance in attention, dysgeusia, dyskinesia, restless legs syndrome, poor quality sleep
  Rare: Serotonin syndrome, convulsions, psychomotor restlessness, extra-pyramidal symptoms
- **Eye disorders**
  Common: Blurred vision
  Uncommon: Mydriasis, visual impairment
  Rare: Glaucoma
- **Ear and labyrinth disorders**
  Common: Tinnitus
  Uncommon: Vertigo, ear pain
- **Cardiac disorders**
  Common: Palpitations
  Uncommon: Tachycardia, supra-ventricular arrhythmia, mainly atrial fibrillation
- **Vascular disorders**
  Common: Blood pressure increase, flushing
  Uncommon: Syncope, hypertension, orthostatic hypotension, peripheral coldness
  Rare: Hypertensive crisis
- **Respiratory, thoracic and mediastinal disorders**
  Common: Yawning
  Uncommon: Throat tightness, epistaxis
- **Gastrointestinal disorders**
  Very common: Nausea, dry mouth
  Common: Constipation, diarrhea, abdominal pain, vomiting, dyspepsia, flatulence
  Uncommon: Gastrointestinal haemorrhage, gastroenteritis, eructation, gastritis, dysphagia
  Rare: Stomatitis, haematochezia, breath odour
- **Hepato-biliary disorders**
  Uncommon: Hepatitis, elevated liver enzymes (ALT, AST, alkaline phosphatase), acute liver injury
  Rare: Hepatic failure, jaundice
- **Skin and subcutaneous tissue disorders**
  Common: Sweating increased, rash
  Uncommon: Night sweats, urticaria, dermatitis contact, cold sweat, photo-sensitivity reactions, increased tendency to bruise
  Rare: Stevens-Johnson Syndrome, angio-neurotic oedema
- **Musculoskeletal and connective tissue disorders**
  Common: Musculo-skeletal pain, muscle spasm
  Uncommon: Muscle tightness, muscle twitching
  Rare: Trismus
- **Renal and urinary disorders**
  Common: Dysuria, pollakiuria
  Uncommon: Urinary retention, urinary hesitation, nocturia, polyuria, urine flow decreased
  Rare: Urine odour abnormal
- **Reproductive system and breast disorders**
  Common: Erectile dysfunction, ejaculation disorder, ejaculation delayed
  Uncommon: Gynaecological haemorrhage, menstrual disorder, sexual dysfunction, testicular pain
  Rare: Menopausal symptoms, galactorrhoea, hyperprolactinaemia
- **General disorders and administration site conditions**
  Common: Falls, fatigue
  Uncommon: Chest pain, feeling abnormal, feeling cold, thirst, chills, malaise, feeling hot, gait disturbance
- **Investigations**
  Common: Weight decrease
  Uncommon: Weight increase, blood creatine phosphokinase increased, blood potassium increased
  Rare: Blood cholesterol increased

OVERDOSE AND TREATMENT

Cases of overdoses, alone or in combination with other medicinal products, with Duloxetine doses of 5400 mg were reported. Some fatalities have occurred, primarily with mixed overdoses, but also with Duloxetine alone at a dose of approximately 1000 mg. 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. 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.

DOSAGE AND ADMINISTRATION

For oral use, with or without food.

Major Depressive Disorder: The starting and recommended maintenance dose is 60 mg once daily with or without food. Dosages above 60 mg once daily, up to a maximum dose of 120 mg per day have been evaluated from a safety perspective in clinical trials. However, there is no clinical evidence suggesting that patients not responding to the initial recommended dose may benefit from dose up-titrations.

Therapeutic response is usually seen after 2-4 weeks of treatment.

After consolidation of the antidepressive response, it is recommended to continue treatment for several months, in order to avoid relapse. In patients responding to Duloxetine, and with a history of repeated episodes of major depression, further long-term treatment at a dose of 60 to 120 mg/day could be considered.

Generalised Anxiety Disorder: For most patients, the recommended starting dose for Cymbalta is 60 mg administered once daily. For some patients, it may be desirable to start at 30 mg once daily for 1 week, to allow patients to adjust to the medication before increasing to 60 mg once daily. While a 120 mg once daily dose was shown to be effective, there is no evidence that doses greater than 60 mg once daily confer additional benefit. Nevertheless, if a decision is made to increase the dose beyond 60 mg once daily, dose increases should be in increments of 30 mg once daily. The safety of doses above 120 mg once daily has not been adequately evaluated.

Diabetic Peripheral Neuropathic Pain: The starting and recommended maintenance dose is 60 mg daily. While a dose up to 120mg/day was shown to be safe and effective, there is no evidence that doses higher than 60mg 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.

Response to treatment should be evaluated after 2 months. In patients with inadequate initial response, additional response after this time is unlikely.

The therapeutic benefit should be reassessed regularly (at least every three months)

Use in elderly: No dosage adjustment is necessary.

Use in renal impairment: No dosage adjustment is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 ml/min). Duloxetine must not be used in patients with severe renal impairment (creatinine clearance <30 ml/min).

Use in hepatic impairment: Duloxetine must not be used in patients with liver disease resulting in hepatic impairment.

Use in paediatric population: Duloxetine should not be used in children and adolescents under the age of 18 years for the treatment of major depressive disorder because of safety and efficacy concerns.The safety and efficacy of Duloxetine for the treatment of generalised anxiety disorder in paediatric patients aged 7-17 years have not been established. The safety and efficacy of Duloxetine for the treatment of diabetic peripheral neuropathic pain has not been studied. No data are available.

Note: The information given here is limited. For further information, kindly consult your doctor or pharmacist.

Storage: Store below 30°C.

Presentation/Packing: PCTFE/PE/PVC blisters with ALU blister pack of 2 x 14's

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