200 mm

186 mm | 14 mm

16 mm | 20 mm | 164 mm

30 mm

320 mm

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Macxetine 30mg / 60mg Capsule

Duloxetine Delayed Release Capsules 30 mg / 60 mg

COMPOSITION

Each delayed release capsule contains :
Duloxetine Hydrochloride
Equivalent to Duloxetine……30 mg / 60 mg

DOSAGE FORM

Oral Hard gelatin capsule

PRODUCT DESCRIPTION

1) 30 mg : Opaque blue cap/opaque white body, size "3" capsules containing white to off- white coloured pellets with "C83" on cap imprinted with white ink.
2) 60 mg : Opaque blue cap/opaque green body, size "1" capsules containing white to off-white coloured pellets with "C81" on cap imprinted with white ink.

PHARMACOLOGICAL CLASSIFICATION

Antidepressants

PHARMACOLOGICAL ACTION:

Pharmacodynamics

ATC Code: N06AX21

Mode 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 normalised pain thresholds in several preclinical models 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

Duloxetine is administered as a single enantiomer. Duloxetine is extensively metabolised by oxidative enzymes (CYP1A2 and the polymorphic CYP2D6), followed by conjugation. The pharmacokinetics of Duloxetine demonstrate large intersubject variability (generally 50-60%), partly due to gender, age, smoking status, and CYP2D6 metaboliser status.

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 alpha,-acid glycoprotein. Protein binding is not affected by renal or hepatic impairment.

Biotransformation: 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. The circulating metabolites of Duloxetine are considered pharmacologically inactive.

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

Special Populations

Renal impairment: End stage renal disease (ESRD) patients receiving dialysis had 2-fold higher Duloxetine C_{max} and AUC values.

Hepatic impairment: Moderate liver disease (Child-Pugh Class B) affected the pharmacokinetics of Duloxetine.

INDICATIONS

Duloxetine Hydrochloride is indicated for:

- Treatment of major depressive disorder.
- Management of neuropathic pain associated with diabetic peripheral neuropathy in adults.
- Treatment of generalised anxiety disorder.

ROUTE OF ADMINISTRATION

Oral

DOSAGE

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 persepective. 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.

Diabetic Peripheral Neuropathic Pain : The starting and recommended maintenance dose is 60 mg daily with or without food. Dosages above 60 mg once daily, up to a maximum dose of 120 mg per day administered in evenly divided doses, have been evaluated from a safety perspective. The plasma concentration of duloxetine displays large inter-individual variability. Hence, some patients that respond insufficiently to 60 mg may benefit from a higher dose. 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).

Generalized Anxiety Disorder :
The recommended starting dose in patients with generalised anxiety disorder is 30 mg once daily with or without food. In patients with insufficient response the dose should be increased to 60 mg, which is the usual maintenance dose in most patients. In patients with co-morbid major depressive disorder, the starting and maintenance dose is 60 mg once daily (please see also dosing recommendation above). Doses up to 120 mg per day have been shown to be efficacious and have been evaluated from a safety perspective. In patients with insufficient response to 60 mg, escalation up to 90 mg or 120 mg may therefore be considered. Dose escalation should be based upon clinical response and tolerability. After consolidation of the response, it is recommended to continue treatment for several months, in order to avoid relapse.

Special Populations :

Elderly: No dosage adjustment is recommended for elderly patients solely on the basis of age. However, as with any medicine, caution should be exercised when treating the elderly, especially with Duloxetine 120 mg per day for major depressive disorder or generalised anxiety disorder, for which data are limited.

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

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).

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.

Discontinuation of treatment:
Abrupt discontinuation should be avoided. When stopping treatment with 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

- 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.
- 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.

ADVERSE REACTION

Frequency estimate: Very common, common , uncommon, rare, very rare

Infections and Infestations:
Uncommon: Laryngitis

Immune System Disorders:
Rare: Anaphylactic reaction, Hyper-sensitivity disorder

Endocrine Disorders:
Rare: Hypothyroidism

Metabolism and Nutrition Disorders:
Common: Decreased appetite
Uncommon: Hyperglycaemia (reported especially in diabetic patients)
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, Diarrhoea, Abdominal pain,
Vomiting, Dyspepsia, Flatulence
Uncommon: Gastrointestinal haemorrhage,
Gastroenteritis, Eructation, Gastritis, Dysphagia
Rare: Stomatitis, Haematochezia, Breath odour, Microscopic colitis

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
Very rare: Cutaneous vasculitis

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: Fatigue, Falls.
Uncommon: Chest pain, Feeling abnormal, Feeling cold, Thirst, Chills, Malaise, Feeling hot, Gait disturbance

200 mm

320 mm

Investigations:
Common: Weight decrease
Uncommon: Weight increase, Blood creatine phosphokinase increased, Blood potassium increased
Rare: Blood cholesterol increased

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. Based on the half-life of Duloxetine, at least 5 days should be allowed after stopping Duloxetine before starting an MAOI.
For selective, reversible MAOIs, like moclobemide, the risk of serotonin syndrome is lower. However, the concomitant use of Duloxetine with selective, reversible MAOIs is not recommended.
Inhibitors of CYP1A2: 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 AUC_{0-t} 6-fold. Therefore, Duloxetine should not be administered in combination with potent inhibitors of CYP1A2 like Fluvoxamine.
CNS Medicinal Products: The risk of using Duloxetine in combination with other CNS-active medicinal products has not been systematically evaluated. Consequently, 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: In rare cases, serotonin syndrome has been reported in patients using SSRIs (e.g., paroxetine, fluoxetine) concomitantly with serotonergic medicinal products. Caution is advisable if Duloxetine is used concomitantly with serotonergic antidepressants like SSRIs, tricyclics like clomipramine or amitriptyline, St John's Wort (*Hypericum perforatum*), venlafaxine, 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).
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 (risperidone, tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), particularly if they have a narrow therapeutic index (such as flecainide, propafenone, and metoprolol).
Oral contraceptives and other steroidal agents: Results of *in vitro* studies demonstrate that Duloxetine does not induce the catalytic activity of CYP3A. Specific *in vivo* drug interaction studies have not been performed.
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. 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, 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:
Antacids and H_2 antagonists: Co-administration of Duloxetine with aluminium- and magnesium-containing antacids, or Duloxetine with Famotidine, had no significant effect on the rate or extent of Duloxetine absorption after administration of a 40 mg oral dose.
Inducers of CYP1A2: Population pharmacokinetic analyses have shown that smokers have almost 50% lower plasma concentrations of Duloxetine compared with non-smokers.

WARNINGS & 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.
Renal Impairment: Increased plasma concentrations of Duloxetine occur in patients with severe renal impairment on haemodialysis (creatinine clearance <30 ml/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.
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:
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. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.
Other psychiatric conditions for which Duloxetine is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.
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.
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.
Diabetic Peripheral Neuropathic Pain: As with other medicinal products with similar pharmacological action (antidepressants), isolated cases of suicidal ideation and suicidal behaviours 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:
Duloxetine should not be used in the treatment of children and adolescents under the age of 18 years.
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.
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: Data on the use of Duloxetine 120 mg in elderly patients with major depressive disorders are limited. Therefore, caution should be exercised when treating the elderly with the maximum dosage. Data on the use of Duloxetine in elderly patients with generalised anxiety disorder are limited.
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 Products Containing Duloxetine: Duloxetine is used under different trademarks in several indications (treatment of diabetic neuropathic pain, major depressive disorder, generalised anxiety disorder and stress urinary incontinence). The use of more than one of these products concomitantly should be avoided.
Hepatitis/Increased Liver Enzymes: Duloxetine should be used with caution in patients treated with other medicinal products associated with hepatic injury.
Suicidality in Children and Adolescents: Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber. The indication(s) approved in paediatric for the particular drug should be clearly stated / included.

Pregnancy & Lactation
Pregnancy:
There are no adequate data on the use of Duloxetine in pregnant women.
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). 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, jitteriness, 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.
Nursing Mothers: 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.
Fertility
Duloxetine had no effect on male fertility, and effects in females were only evident at doses that caused maternal toxicity.

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. 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.
STORAGE
Store below 30°C in a dry place, protect from light.
KEEP OUT OF REACH OF CHILDREN.

PRESENTATION
Alu/Alu Blister pack of 10 Capsules. Such 3 blisters are packed in a carton along with a pack insert.
Alu/Alu Blister pack of 10 Capsules. Such 10 blisters are packed in a carton along with a pack insert.

MACLEODS

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