Loxyt®

Duloxetine Hydrochloride

FORMS AND PRESENTATION

Loxyt® 30: Delayed release capsules: Box of 30.

Loxyt® 60: Delayed release capsules: Box of 30.

COMPOSITION

Loxyt® 30: Each delayed release capsule contains Duloxetine Hydrochloride Eq. to Duloxetine 30mg.

Loxyt® 60: Each delayed release capsule contains Duloxetine Hydrochloride Eq. to Duloxetine 60mg.

Excipients: Sucrose, starch, hypromellose, crospovidone, talc, carboxy methyl ethyl cellulose, povidone, titanium dioxide, polyethylene glycol, polysorbate, gelatin, indigotine, yellow iron oxide (Loxyt 60).

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Therapeutic class: Psychoanaleptics.

ATC code: N06AX21.

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 behavior 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.

Pharmacokinetic properties

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 alpha1-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 catalyze 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 intravenous dose the plasma clearance of Duloxetine ranges from 22 l/hr to 46 l/hr (mean of 36 l/hr). After an oral dose the apparent plasma clearance of Duloxetine ranges from 33 to 261 l/hr (mean 101 l/hr).

INDICATIONS

Loxyt® is indicated in adults.

- Treatment of major depressive disorder.
- Treatment of diabetic peripheral neuropathic pain.
- Treatment of generalized anxiety disorder.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- 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.

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.
- Renal impairment: Increased plasma concentrations of Duloxetine occur in patients with severe renal impairment on hemodialysis (creatinine clearance <30 ml/min).
- Use with antidepressants: Caution should be exercised when using Duloxetine in combination with antidepressants. In particular, the combination with selective reversible MAOIs is not recommended.
- 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: Depression (Major Depressive Disorder and Generalized Anxiety Disorder) 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 behavior, 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 behavior or thoughts, and unusual changes in behavior, 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 behaviors 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: No clinical trials have been conducted with Duloxetine in pediatric populations. Duloxetine should not be used in the treatment of children and adolescents under the age of 18 years.
- Hemorrhage: There have been reports of bleeding abnormalities, such as ecchymoses, purpura, and gastrointestinal hemorrhage, 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.
- Hyponatremia: Hyponatremia has been reported when administering Duloxetine, including cases with serum sodium lower than 110 mmol/l. Hyponatremia may be due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH). The majority of cases of hyponatremia 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 hyponatremia, 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.
- 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, generalized anxiety disorder and stress urinary incontinence). The use of more than one of these products concomitantly 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.

Ability to drive and use machines:

No studies of the effects on the ability to drive and use machines have been performed. Duloxetine may be associated with sedation and dizziness. Patients should be instructed that if they experience sedation or dizziness they should avoid potentially hazardous tasks such as driving or operating machinery.

PREGNANCY AND LACTATION

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 fetus. Women should be advised to notify their physician if they become pregnant, or intend to become pregnant, during therapy.

Duloxetine is very weakly excreted into human milk. 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.

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, except in the cases described in this section. 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.
- 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. When Duloxetine was administered at a dose of 60 mg twice daily with a single dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. The co-administration of Duloxetine (40 mg twice daily) increases steady-state AUC of tolterodine (2 mg twice daily) by 71%, but does not affect the pharmacokinetics of its active 5-hydroxyl metabolite and no dosage adjustment is recommended. 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, 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.
- Antacids and H2 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.

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 ($\geq$1/10), common ($\geq$1/100 to <1/10), uncommon ($\geq$1/1,000 to <1/100), rare ($\geq$1/10,000 to <1/1,000), very rare (<1/10,000).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness:

- Infections and infestations: laryngitis (uncommon)
- Immune system disorders: anaphylactic reaction, hyper-sensitivity disorder (rare)
- Endocrine disorders: hypo-thyroidism (rare)
- Metabolism and nutrition disorders: decreased appetite (common); hyperglycemia in diabetic patients (uncommon); dehydration, hyponatremia, SIADH (rare)
- Psychiatric disorders: insomnia, agitation, decreased libido, anxiety, abnormal orgasm, abnormal dreams (common); suicidal ideation, sleep disorder, bruxism, disorientation, apathy (uncommon); suicidal behavior, mania, hallucinations, aggression and anger (rare)
- Nervous system disorders: headache, somnolence (very common); dizziness, lethargy, tremor, paresthesia (common); myoclonus, akathisia, nervousness, disturbance in attention, dysgeusia, dyskinesia, restless leg syndrome, poor quality sleep (uncommon); serotonin syndrome, convulsions, psychomotor restlessness, extra-pyramidal symptoms (rare)
- Eye disorders: blurred vision (common); mydriasis, visual impairment (uncommon); glaucoma (rare)
- Ear and labyrinth disorders: tinnitus (common); vertigo, ear pain (uncommon)
- Cardiac disorders: palpitations (common); tachycardia, supra-ventricular arrhythmia, mainly atrial fibrillation (uncommon)
- Vascular disorders: increased blood pressure, flushing (common); syncope, hypertension, orthostatic hypotension, peripheral coldness (uncommon) hypertensive crisis (rare)
- Respiratory, thoracic and mediastinal disorders: yawning (common); throat tightness, epistaxis (uncommon)
- Gastrointestinal disorders: nausea, dry mouth (very common); constipation, diarrhea, abdominal pain, vomiting, dyspepsia, flatulence (common); gastrointestinal hemorrhage, gastroenteritis, eructation, gastritis (uncommon); stomatitis, hematochezia, breath odor (rare)
- Hepato-biliary disorders: hepatitis, elevated liver enzymes, acute liver injury (uncommon), hepatic failure, jaundice (rare)
- Skin and subcutaneous tissue disorders: increased sweating, rash (common); night sweats, urticaria, dermatitis contact, cold sweat, photo-sensitivity reactions, increased tendency to bruise (uncommon); Stevens-Johnson Syndrome, angio-neurotic edema (rare)
- Musculoskeletal and connective tissue disorders: musculo-skeletal pain, muscle spasm (common); muscle tightness, muscle twitching (uncommon); trismus (rare)
- Renal and urinary disorders: dysuria (common); urinary retention, urinary hesitation, nocturia, polyuria, urine flow decreased (uncommon); urine odor abnormal (rare)
- Reproductive system and breast disorders: erectile dysfunction, ejaculation disorder, ejaculation delayed (common); gynecological hemorrhage, menstrual disorder, sexual dysfunction (uncommon); menopausal symptoms, galactorrhea, hyperprolactinemia (rare)
- General disorders and administration site conditions: fatigue (common); chest pain, falls, feeling abnormal, feeling cold, thirst, chills, malaise, feeling hot, gait disturbance (uncommon)
- Investigations: weight decrease (common); weight increase, increased blood creatine phosphokinase, increased blood potassium (uncommon); increased blood cholesterol (rare)

Discontinuation of Duloxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paresthesia), sleep disturbances (including insomnia and intense dreams), fatigue, somnolence, agitation or anxiety, nausea and/or vomiting, tremor, headache, irritability, diarrhea, hyperhydrosis and vertigo are the most commonly reported reactions.

Generally, for SSRIs and SNRIs, these events are mild to moderate and self-limiting; however, in some patients they may be severe and/or prolonged. It is therefore advised that when Duloxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out.

DOSAGE AND ADMINISTRATION

- 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 Loxyt®, 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.

- Generalized Anxiety Disorder: The recommended starting dose in patients with generalized 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.

Doses up to 120 mg per day have been shown to be efficacious and have been evaluated from a safety perspective in clinical trials. 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.

- 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 in clinical trials. The plasma concentration of Loxyt® 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).

Hepatic Impairment

Loxyt® 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). Loxyt® must not be used in patients with severe renal impairment (creatinine clearance <30 ml/min).

Discontinuation of Treatment

Abrupt discontinuation should be avoided. When stopping treatment with Loxyt® 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.

OVERDOSAGE

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, hemoperfusion, and exchange perfusion are unlikely to be beneficial.

STORAGE CONDITIONS

Store below 30°C.

Keep in original pack in intact conditions.

Date of revision: August 2016.

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

Benta S.A.L.
Dbayeh - Lebanon