150 mm

OBS

C-YALTA™ CAPSULES

(Duloxetine)

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(ڈیولوکسٹین)

C-YALTA CAPSULES 20mg:
Each capsule contains:
Duloxetine HCl enteric coated pellets eq. to
Duloxetine U.S.P. 20mg

C-YALTA CAPSULES 30mg:
Each capsule contains:
Duloxetine HCl enteric coated pellets eq. to
Duloxetine U.S.P. 30mg

C-YALTA CAPSULES 60mg:
Each capsule contains:
Duloxetine HCl enteric coated pellets eq. to
Duloxetine U.S.P. 60mg

PHARMACOLOGICAL PROPERTIES:

Pharmacodynamic properties:
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.

Major Depressive Disorder:
Duloxetine was studied in a clinical programme involving 3,158 patients (1,285 patient-years of exposure) meeting DSM-IV criteria for major depression. The efficacy of duloxetine at the recommended dose of 60 mg once a day was demonstrated in three out of three randomised, double-blind, placebo-controlled, fixed-dose acute studies in adult outpatients with major depressive disorder. Overall, duloxetine's efficacy has been demonstrated at daily doses between 60 and 120 mg in a total of five out of seven randomised, double-blind, placebo-controlled, fixed-dose acute studies in adult outpatients with major depressive disorder. Duloxetine demonstrated statistical superiority over placebo as measured by improvement in the 17-item Hamilton Depression Rating Scale (HAM-D) total score (including both the emotional and somatic symptoms of depression). Response and remission rates were also statistically significantly higher with duloxetine compared with placebo. Only a small proportion of patients included in pivotal clinical trials had severe depression (baseline HAM-D >25).

In a relapse prevention study, patients responding to 12 weeks of acute treatment with open-label duloxetine 60 mg once daily were randomised to either duloxetine 60 mg once daily or placebo for a further 6 months. Duloxetine 60 mg once daily demonstrated a statistically significant superiority compared to placebo ($p = 0.004$) on the primary outcome measure, the prevention of depressive relapse, as measured by time to relapse. The incidence of relapse during the 6-months double-blind, follow-up period was 17% and 29% for duloxetine and placebo, respectively. During 52 weeks of placebo-controlled double-blind treatment, duloxetine-treated patients with recurrent MDD had a significantly longer symptom free period ($p<.001$) compared with patients randomised to placebo. All patients had previously responded to duloxetine during open-label duloxetine treatment (28 to 34 weeks) at a dose of 60 to 120 mg/day. During the 52-week placebo-controlled double-blind treatment phase, 14.4% of the duloxetine-treated patients and 33.1% of the placebo-treated patients experience a return of their depressive symptoms ($p<.001$). The effect of duloxetine 60 mg once a day in elderly depressed patients (≥ 65 years) was specifically examined in a study that showed a statistically significative difference in the reduction of the HAM-D17 score for duloxetine-treated patients compared to placebo. Tolerability of duloxetine 60 mg once daily in elderly patients was comparable to that seen in the younger adults. However, data on elderly patients exposed to the maximum dose (120 mg per day) are limited and thus, caution is recommended when treating this population.

Generalised Anxiety Disorder:
Duloxetine demonstrated statistically significant superiority over placebo in five out of five studies including four randomised, double-blind, placebo-controlled acute studies and a relapse prevention study in adult patients with generalised anxiety disorder. Duloxetine demonstrated statistically significant superiority over placebo as measured by improvement in the Hamilton Anxiety Scale (HAM-A) total score and by the Sheehan Disability Scale (SDS) global functional impairment score.

Response and remission rates were also higher with duloxetine compared to placebo. Duloxetine showed comparable efficacy results to venlafaxine in terms of improvements on the HAM- A total score. In a relapse prevention study, patients responding to 6 months of acute treatment with open-label duloxetine were randomised to either duloxetine or placebo for a further 6 months. Duloxetine 60 mg to 120 mg once daily demonstrated statistically significant superiority compared to placebo ($p<0.001$) on the prevention of relapse, as measured by time to relapse. The incidence of relapse during the 6-months double-blind, follow-up period was 14% for duloxetine and 42% for placebo.

Diabetic Peripheral Neuropathic Pain:
The efficacy of duloxetine as a treatment for diabetic neuropathic pain was established in 2 randomised, 12- week, double-blind, placebo-controlled, fixed-dose studies in adults (22 to 88 years) having diabetic neuropathic pain for at least 6 months. Patients meeting diagnostic criteria for major depressive disorder were excluded from these trials. The primary outcome measure was the weekly mean of 24-hour average pain, which was collected in a daily diary by patients on an 11-point Likert scale. In both studies, duloxetine 60 mg once daily and 60 mg twice daily significantly reduced pain compared with placebo. The effect in some patients was apparent in the first week of treatment. The difference in mean improvement between the two active treatment arms was not significant. At least 30% reported pain reduction was recorded in approximately 65% of duloxetine-treated patients versus 40% for placebo. The corresponding figures for at least 50% pain reduction were 50% and 26%, respectively. Clinical response rates (50% or greater improvement in pain) were analysed according to whether or not the patient experienced somnolence during treatment. For patients not experiencing somnolence, clinical response was observed in 47% of patients receiving duloxetine and 27% of patients on placebo. Clinical response rates in patients experiencing somnolence were 60% on duloxetine and 30% on placebo. Patients not demonstrating a pain reduction of 30% within 60 days of treatment were unlikely to reach this level during further treatment. In an open-label, long-term uncontrolled study, the pain reduction in patients responding to 8 weeks of acute treatment of duloxetine 60 mg once daily was maintained for a further 6 months as measured by change on the Brief Pain Inventory (BPI) 24-hour average pain item.

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 Cmax 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 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.

210 mm

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).

Special Populations:

Gender: Pharmacokinetic differences have been identified between males and females (apparent plasma clearance is approximately 50% lower in females). Based upon the overlap in the range of clearance, gender-based pharmacokinetic differences do not justify the recommendation for using a lower dose for female patients.

Age:
Pharmacokinetic differences have been identified between younger and elderly females (≥ 65 years) (AUC increases by about 25% and half-life 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 had 2-fold higher duloxetine Cmax and AUC values compared with healthy subjects. Pharmacokinetic data on duloxetine is limited in patients with mild or moderate renal impairment.

Hepatic impairment:
Moderate liver disease (Child-Pugh Class B) affected the pharmacokinetics of duloxetine. Compared with healthy subjects, the apparent plasma clearance of duloxetine was 79% lower, the apparent terminal half-life was 2.3-times longer, and the AUC was 3.7-times higher in patients with moderate liver disease. The pharmacokinetics of duloxetine and its metabolites have not been studied in patients with mild or severe hepatic insufficiency.

Breast-feeding mothers:
The disposition of duloxetine was studied in 6 lactating women who were at least 12-weeks postpartum. Duloxetine is detected in breast milk, and steady-state concentrations in breast milk are about one-fourth those in plasma. The amount of duloxetine in breast milk is approximately 7µg/day while on 40 mg twice-daily dosing. Lactation did not influence duloxetine pharmacokinetics.

Preclinical safety data:
Duloxetine was not genotoxic in a standard battery of tests and was not carcinogenic in rats. Multinucleated cells were seen in the liver in the absence of other histopathological changes in the rat carcinogenicity study. The underlying mechanism and the clinical relevance are unknown. Female mice receiving duloxetine for 2 years had an increased incidence of hepatocellular adenomas and carcinomas at the high dose only (144 mg/kg/day), but these were considered to be secondary to hepatic microsomal enzyme induction. The relevance of this mouse data to humans is unknown. Female rats receiving duloxetine (45 mg/kg/day) before and during mating and early pregnancy had a decrease in maternal food consumption and body weight, oestrous cycle disruption, decreased live birth indices and progeny survival, and progeny growth retardation at systemic exposure levels estimated to be at the most at maximum clinical exposure (AUC). In an embryotoxicity study in the rabbit, a higher incidence of cardiovascular and skeletal malformations was observed at systemic exposure levels below the maximum clinical exposure (AUC). No malformations were observed in another study testing a higher dose of a different salt of duloxetine. In prenatal/postnatal toxicity studies in the rat, duloxetine induced adverse behavioural effects in the offspring at exposures below maximum clinical exposure (AUC).

INDICATIONS:
- Treatment of major depressive disorder.
- Treatment of diabetic peripheral neuropathic pain in adults.
- Treatment of generalised anxiety disorder.

CONTRAINDICATIONS:
Hypersensitivity to the active substance or to any of the excipients. Concomitant use of C-YALTA (Duloxetine) with non-selective, irreversible monoamine oxidase inhibitors (MAOIs) is contraindicated. Liver disease resulting in hepatic impairment. C-YALTA (Duloxetine) should not be used in combination with fluvoxamine, ciprofloxacin or enoxacine (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 C-YALTA (Duloxetine) is contraindicated in patients with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis.

INTERACTIONS:

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 C-YALTA (Duloxetine) is taken in combination with other centrally-acting medicinal products and substances, including alcohol and sedative medicinal products (e.g., benzodiazepines, morphinomimetics, antipsychotics, phenobarbital, and sedative antihistamines).

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 C-YALTA (Duloxetine) before starting an MAOI. For selective, reversible MAOIs, like moclobemide, the risk of serotonin syndrome is lower. However, the concomitant use of C-YALTA (Duloxetine) with selective, reversible MAOIs is not recommended.

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 C-YALTA (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. 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 C-YALTA (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.

Effects of Other Medicinal Products on Duloxetine:

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.

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 AUCo-t 6-fold. Therefore, C-YALTA (Duloxetine) should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine.

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

PRECAUTIONS:
Mania and Seizures: C-YALTA (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 C-YALTA (Duloxetine) to patients with increased intra-ocular 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).

Use with Antidepressants:
Caution should be exercised when using C-YALTA (Duloxetine) in combination with antidepressants. In particular the combination with selective reversible MAOIs is not recommended.

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. Concerning risk factors for suicidality in depression, see above. 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 paediatric populations. C-YALTA (Duloxetine) should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempts and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour, and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation, and cognitive and behavioural development are lacking.

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.

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. As with other serotonergic medicinal products, discontinuation symptoms may occur in the neonate after maternal duloxetine use near term. C-YALTA (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.

Breast-Feeding:
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 C-YALTA (Duloxetine) while breast-feeding is not recommended.

ADVERSE REACTIONS :
Adverse reactions may include: Appetite changes, constipation,diarrhea, dizziness, dry mouth, fatigue, headache, insomnia, nausea, sexual difficulties, sleepiness, sweating, tremor, urinary difficulties, vomiting, weakness.

DOSAGE AND ADMINISTRATION:

Adults:

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:
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. 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 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).

Method of Administration: For oral use.

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 C-YALTA (Duloxetine) 120 mg per day for major depressive disorder, for which data are limited.

Children and Adolescents:
Duloxetine is not recommended for use in children and adolescents due to insufficient data on safety and efficacy.

Hepatic Impairment:
C-YALTA (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). C-YALTA (Duloxetine) 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 C-YALTA (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.

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

INSTRUCTIONS:
- To be sold on the prescription of a registered medical practitioner only.
- Store below 25°C.
- Protect from heat, light and moisture.
- Keep out of the reach of children.

PRESENTATION:
- 20mg capsules: C-YALTA CAPSULES 20mg in the blister pack of 1 x 10's.
- 30mg capsules: C-YALTA CAPSULES 30mg in the blister pack of 1 x 10's.
- 60mg capsules: C-YALTA CAPSULES 60mg in the blister pack of 1 x 10's.

MANUFACTURED BY:

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CIR-CLT-0514