ASPIN
An OBS Group Company

C-yalta® Capsule سی-یالٹا کیپسول

(Duloxetine)

QUALITATIVE & QUANTITATIVE COMPOSITION

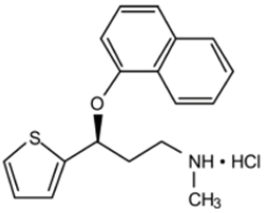
C-yalta Capsules 20mg:
Each capsule contains:
Duloxetine HCl (enteric coated pellets) equivalent to
Duloxetine.....20 mg.

C-yalta Capsules 30mg:
Each capsule contains:
Duloxetine HCl (enteric coated pellets) equivalent to
Duloxetine.....30 mg.

C-yalta Capsules 60mg:
Each capsule contains:
Duloxetine HCl (enteric coated pellets) equivalent to
Duloxetine.....60 mg.

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS
Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older. In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber.

DESCRIPTION:
CYALTA (duloxetine hydrochloride) is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) for oral administration. Its chemical designation is (+)-(S)-N-methyl-γ-(1-naphthyloxy) 2-thiophenepropylamine hydrochloride. The empirical formula is $C_{18}H_{19}NOS$•HCl, which corresponds to a molecular weight of 333.88. The structural formula is:



CLINICAL INFORMATION
INDICATIONS:

- Major Depressive Disorder
- Generalized Anxiety Disorder
- Diabetic Peripheral Neuropathic Pain
- Fibromyalgia
- Chronic Musculoskeletal Pain

DOSAGE AND ADMINISTRATION
Dosage for Treatment of Major Depressive Disorder
Administer CYALTA at a total dose of 40 mg/day (given as 20 mg twice daily) to 60 mg/day (given either once daily or as 30 mg twice 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/day dose was shown to be effective, there is no evidence that doses greater than 60 mg/day confer any additional benefits. The safety of doses above 120 mg/day has not been adequately evaluated. Periodically reassess to determine the need for maintenance treatment and the appropriate dose for such treatment

Dosage for Treatment of Generalized Anxiety Disorder
Adults — For most patients, initiate CYALTA 60 mg 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/day confer additional benefit. Nevertheless, if a decision is made to increase the dose beyond 60 mg once daily, increase dose in increments of 30 mg once daily. The safety of doses above 120 mg once daily has not been adequately evaluated. Periodically reassess to determine the continued need for maintenance treatment and the appropriate dose for such treatment.

Elderly — Initiate CYALTA at a dose of 30 mg once daily for 2 weeks before considering an increase to the target dose of 60 mg. Thereafter, patients may benefit from doses above 60 mg once daily. If a decision is made to increase the dose beyond 60 mg once daily, increase dose in increments of 30 mg once daily. The maximum dose studied was 120 mg per day. Safety of doses above 120 mg once daily has not been adequately evaluated.

Children and Adolescents (7 to 17 years of age) — Initiate CYALTA at a dose of 30 mg once daily for 2 weeks before considering an increase to 60 mg. The recommended dose range is 30 to 60 mg once daily. Some patients may benefit from doses above 60 mg once daily. If a decision is made to increase the dose beyond 60 mg once daily, increase dose in increments of 30 mg once daily. The maximum dose studied was 120 mg per day. The safety of doses above 120 mg once daily has not been evaluated

Dosage for Treatment of Diabetic Peripheral Neuropathic Pain
Adult— 60 mg once daily. There is no evidence that doses higher than 60 mg 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, consider a lower starting dose and gradual increase in dose for patients with renal impairment.

Dosage for Treatment of Fibromyalgia
Administer CYALTA 60 mg once daily. Begin treatment at 30 mg once daily for 1 week, to allow patients to adjust to the medication before increasing to 60 mg once daily. Some patients may respond to the starting dose. There is no evidence that doses greater than 60 mg/day confer additional benefit, even in patients who do not respond to a 60 mg dose, and higher doses are associated with a higher rate of adverse reactions.

Dosage for Treatment of Chronic Musculoskeletal Pain
Administer CYALTA 60 mg once daily. Begin treatment at 30 mg for one week, to allow patients to adjust to the medication before increasing to 60 mg once daily. There is no evidence that higher doses confer additional benefit, even in patients who do not respond to a 60 mg dose, and higher doses are associated with a higher rate of adverse reactions.

Dosing in Special Populations
Hepatic Impairment — Avoid use in patients with chronic liver disease or cirrhosis.
Severe Renal Impairment — Avoid use in patients with severe renal impairment, GFR <30 mL/min.

Discontinuing CYALTA
A gradual reduction in dosage rather than abrupt cessation is recommended whenever possible.
Switching a Patient to or from a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders
At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with CYALTA. Conversely, at least 5 days should be allowed after stopping CYALTA before starting an MAOI intended to treat psychiatric disorders.
Use of CYALTA with Other MAOIs such as Linezolid or Methylene Blue
Do not start CYALTA in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome.

CONTRAINDICATIONS:

Monoamine Oxidase Inhibitors

The use of MAOIs intended to treat psychiatric disorders with CYALTA or within 5 days of stopping treatment with CYALTA is contraindicated because of an increased risk of serotonin syndrome. The use of CYALTA within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated. Starting CYALTA in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome

WARNINGS AND PRECAUTIONS

Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that discontinuation can be associated with certain symptoms.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. **Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and non-psychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for CYALTA should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.**

Hepatotoxicity

CYALTA should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established.

Orthostatic Hypotension and Syncope

Orthostatic hypotension and syncope have been reported with therapeutic doses of duloxetine. Syncope and orthostatic hypotension tend to occur within the first week of therapy but can occur at any time during duloxetine treatment, particularly after dose increases. The risk of blood pressure decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as anti-hypertensive) or are potent CYP1A2 inhibitors and in patients taking duloxetine at doses above 60 mg daily. Consideration should be given to discontinuing duloxetine in patients who experience symptomatic orthostatic hypotension and/or syncope during duloxetine therapy.

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, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, and hyperthermia), neuromuscular aberrations (e.g., hyper-reflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, and diarrhea). 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.

Increased Risk of Bleeding

Drugs that interfere with serotonin reuptake inhibition, may increase the risk of bleeding events. Studies have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Other bleeding events related to SSRI and SNRI use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life threatening hemorrhages. Concomitant use of aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anti-coagulants may add to this risk. Patients should be cautioned about the risk of bleeding associated with the concomitant use of duloxetine and NSAIDs, aspirin, or other drugs that affect coagulation.

Severe Skin Reactions

Severe skin reactions, including erythema multiforme and Stevens-Johnson Syndrome (SJS), can occur with Duloxetine. It should be discontinued at the first appearance of blisters, peeling rash, mucosal erosions, or any other sign of hypersensitivity if no other etiology can be identified.

Discontinuation of Treatment with CYALTA

Discontinuation symptoms have been systematically evaluated in patients taking duloxetine. Following abrupt or tapered discontinuation in placebo-controlled clinical trials, the following symptoms occurred at 1% or greater and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness, nausea, headache, paresthesia, fatigue, vomiting, irritability, insomnia, diarrhea, anxiety, and hyperhidrosis. During marketing of other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe. Patients should be monitored for these symptoms when discontinuing treatment with CYALTA. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. 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.

Activation of Mania/Hypomania

In placebo-controlled trials in patients with major depressive disorder, activation of mania or hypomania was reported in 0.1% (2/2,489) of duloxetine-treated patients. Activation of mania or hypomania has been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs effective in the treatment of major depressive disorder. As with these other agents, CYALTA should be used cautiously in patients with a history of mania.

Angle-Closure Glaucoma

The pupillary dilation that occurs following use of many antidepressant drugs including Duloxetine may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

Seizures

Duloxetine has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. In placebo-controlled clinical trials, seizures/convulsions occurred in 0.02% of patients treated with CYALTA and 0.01% (1/9513) of patients treated with placebo. CYALTA should be prescribed with care in patients with a history of a seizure disorder.

Effect on Blood Pressure

In placebo-controlled clinical trials across indications from baseline to endpoint, duloxetine treatment was associated with mean increases of 0.5 mm Hg in systolic blood pressure and 0.8 mm Hg in diastolic blood pressure compared to mean decreases of 0.6 mm Hg systolic and 0.4 mm Hg diastolic in placebo-treated patients. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment.

Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including duloxetine. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported and appeared to be reversible when CYALTA was discontinued. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who is otherwise volume depleted may be at greater risk. Discontinuation of CYALTA should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. More severe and/or acute cases have been associated with hallucination, syncope, seizure, coma, respiratory arrest, and death.

Glycemic Control in Patients with Diabetes

As observed in DPNP trials, duloxetine treatment worsens glycemic control in some patients with diabetes. In three clinical trials of CYALTA for the management of neuropathic pain associated with diabetic peripheral neuropathy, the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 176 mg/dL, and the mean baseline hemoglobin A1C (HbA1c) was 7.8%.

Urinary Hesitation and Retention

Duloxetine is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during treatment with CYALTA, consideration should be given to the possibility that they might be drug-related. In post marketing experience, cases of urinary retention have been observed. In some instances of urinary retention associated with duloxetine use, hospitalization and/or catheterization has been needed.

DRUG INTERACTIONS

Both CYP1A2 and CYP2D6 are responsible for CYALTA metabolism.

Potential for Other Drugs to Affect CYALTA

CYP1A2 Inhibitors — Co-administration of CYALTA with potent CYP1A2 inhibitors should be avoided.

CYP2D6 Inhibitors — Because CYP2D6 is involved in CYALTA metabolism, concomitant use of CYALTA with potent inhibitors of CYP2D6 would be expected to, and does, result in higher concentrations (on average of 60%) of CYALTA.

Potential for CYALTA to Affect Other Drugs

Drugs Metabolized by CYP2D6 — Co-administration of CYALTA with drugs that are extensively metabolized by CYP2D6 and that have a narrow therapeutic index, including certain antidepressants (tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), phenothiazine and Type 1C anti-arrhythmic (e.g., propafenone, flecainide), should be approached with caution. Plasma TCA concentrations may need to be monitored and the dose of the TCA may need to be reduced if a TCA is co-administered with CYALTA. Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, CYALTA and thioridazine should not be co-administered.

Other Clinically Important Drug Interactions

Alcohol — Use of CYALTA concomitantly with heavy alcohol intake may be associated with severe liver injury. For this reason, CYALTA should not be prescribed for patients with substantial alcohol use.

CNS Acting Drugs — Given the primary CNS effects of CYALTA , it should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action

Use in Special Populations:

Pediatric Use

Generalized Anxiety Disorder — In pediatric patients aged 7 to 17 years, efficacy was demonstrated in one 10¬ week, placebo-controlled trial. The safety and effectiveness in pediatric patients less than 7 years of age have not been established.

Major Depressive Disorder — The safety and effectiveness in pediatric patients less than 7 years of age have not been established. The most frequently observed adverse reactions in the clinical trials included nausea, headache, decreased weight, and abdominal pain. Decreased appetite and weight loss have been observed in association with the use of SSRIs and SNRIs. Perform regular monitoring of weight and growth in children and adolescents treated with an SNRI such as CYALTA. Use of CYALTA in a child or adolescent must balance the potential risks with the clinical need.

Geriatric

In the MDD, DPNP, FM, OA, and CLBP studies, no overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. SSRIs and SNRIs, including duloxetine have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event the patient is not necessary. Dosage modifications are not recommended based on gender or for smokers.

Pregnancy & Breastfeeding

Pregnancy

Pregnancy - Category C

There are no adequate and well-controlled studies in pregnant women; therefore, CYALTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Breastfeeding Mothers

Duloxetine is excreted into the milk of lactating women. As the safety of duloxetine in infants is not known, the use of CYALTA; while breast-feeding is not recommended.

ADVERSE REACTIONS:

The following serious adverse reactions are mentioned below:

- Suicidal Thoughts and Behaviors in Children, Adolescents and Young Adults
- Hepatotoxicity
- Orthostatic Hypotension, Falls and Syncope
- Serotonin Syndrome
- Abnormal Bleeding
- Severe Skin Reactions
- Discontinuation of Treatment with CYALTA
- Activation of Mania/Hypomania
- Angle-Closure Glaucoma
- Seizures
- Effect on Blood Pressure
- Clinically Important Drug Interactions
- Hyponatremia
- Urinary Hesitation and Retention

  For details of above list refer to Warning and Precautions

OVER DOSAGE:

In postmarketing experience, fatal outcomes have been reported for acute overdoses, primarily with mixed overdoses, but also with duloxetine only, at doses as low as 1000 mg. Signs and symptoms of overdose (duloxetine alone or with mixed drugs) included somnolence, coma, serotonin syndrome, seizures, syncope, tachycardia, hypotension, hypertension, and vomiting. There is no specific antidote to CYALTA, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. In case of acute overdose, treatment should consist of those general measures employed in the management of overdose with any drug.

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antidepressant drugs ; ATC Code: N06AX21

Mechanism of Action

Although the exact mechanisms of the antidepressant, central pain inhibitory and anxiolytic actions of duloxetine in humans are unknown, these actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS.

Pharmacodynamics

Duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake. Duloxetine has no significant affinity for dopaminergic, adrenergic, cholinergic, histaminergic, opioid, glutamate, and GABA receptors in vitro. Duloxetine does not inhibit monoamine oxidase (MAO). CYALTA is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during treatment with CYALTA, consideration should be given to the possibility that they might be drug-related.

Pharmacokinetics

Duloxetine has an elimination half-life of about 12 hours (range 8 to 17 hours) and their pharmacokinetics is dose proportional over the therapeutic range. Steady-state plasma concentrations are typically achieved after 3 days of dosing. Elimination of duloxetine is mainly through hepatic metabolism involving two P450 isozymes, CYP1A2 and CYP2D6.

Absorption and Distribution

Orally administered duloxetine hydrochloride is well absorbed. There is a median 2 hour lag until absorption begins (Tlag), with maximal plasma concentrations (C_{max}) of duloxetine occurring 6 hours post dose. Food does not affect the Cmax of duloxetine, but delays the time to reach peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (AUC) by about 10%. There is a 3 hour delay in absorption and a one-third increase in apparent clearance of duloxetine after an evening dose as compared to a morning dose. Duloxetine is highly bound (>90%) to proteins in human plasma, binding primarily to albumin and α 1-acid glycoprotein. The interaction between duloxetine and other highly protein bound drugs has not been fully evaluated. Plasma protein binding of duloxetine is not affected by renal or hepatic impairment.

Metabolism and Elimination

Biotransformation and disposition of duloxetine in humans have been determined following oral administration of 14C-labeled duloxetine. Duloxetine comprises about 3% of the total radiolabeled material in the plasma, indicating that it undergoes extensive metabolism to numerous metabolites. The major biotransformation pathways for duloxetine involve oxidation of the naphthyl ring followed by conjugation and further oxidation. Both CYP1A2 and CYP2D6 catalyze the oxidation of the naphthyl ring. Metabolites found in plasma include 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate. Many additional metabolites have been identified in urine, some representing only minor pathways of elimination. Only trace (<1% of dose) amounts of unchanged duloxetine are present in the urine. Most (about 70%) of the duloxetine dose appears in the urine as metabolites of duloxetine; about 20% is excreted in the feces. Duloxetine undergoes extensive metabolism, but the major circulating metabolites have not been shown to contribute significantly to the pharmacologic activity of duloxetine.

PHARMACEUTICAL INFORMATION

Shelf life

2 years.

Special Precautions for Storage

- To be sold on the prescription of a registered medical practitioner only.
- Do not store above 30° C.
- Protect from light and moisture.
- Keep out of the reach of children.

Nature and Contents of Container

C-yalta (Duloxetine) 20mg capsules are supplied in the blister pack of 10's (1x10's).

C-yalta (Duloxetine) 30mg capsules are supplied in the blister pack of 10's (1x10's).

C-yalta (Duloxetine) 60mg capsules are supplied in the blister pack of 10's (1x10's).

MANUFACTURED BY:

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REVISION DATE: December 2019

ہدایات:

صرف مستند ڈاکٹر کے نسخے پر فروخت کریں۔

۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں۔

دوا کو روشنی اور نمی سے محفوظ رکھیں۔ بچوں کی پہنچ سے دور رکھیں۔