583-2016-05
Duloxetine Delayed-Release Capsules, USP
2035596

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DULOXETINE DELAYED-RELEASE CAPSULES safely and effectively. See full prescribing information for DULOXETINE DELAYED-RELEASE CAPSULES.

DULOXETINE delayed-release capsules, for oral use.

Initial U.S. Approval: 2004

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- **Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants (5.1)**
- **Monitor for worsening and emergence of suicidal thoughts and behaviors (5.1)**

----------RECENT MAJOR CHANGES----------

Boxed Warning: Suicidal Thoughts and Behaviors	10/2014
Indications and Usage (1)	10/2014
Dosage and Administration:	
Dosage for Treatment of Generalized Anxiety Disorder (2.2)	10/2014
Contraindications:	
Uncontrolled Narrow-Angle Glaucoma (4.2) Removed	07/2014
Warnings and Precautions:	
Orthostatic Hypotension, Falls and Syncope (5.3)	11/2014
Angle-Closure Glaucoma (5.9)	07/2014

----------INDICATIONS AND USAGE----------

Duloxetine delayed-release capsules, USP is a serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for:

- Major Depressive Disorder (MDD) (1)
- Generalized Anxiety Disorder (GAD) (1)
- Diabetic Peripheral Neuropathic Pain (DPNP) (1)
- Chronic Musculoskeletal Pain (1)

----------DOSAGE AND ADMINISTRATION----------

- Take duloxetine delayed-release capsules once daily, with or without food. Swallow duloxetine delayed-release capsules whole; do not crush or chew, do not open capsule. Take a missed dose as soon as it is remembered. Do not take two doses of duloxetine delayed-release capsules at the same time. (2)

Indication	Starting Dose	Target Dose	Maximum Dose
MDD (2.1)	40 mg/day to 60 mg/day	Acute Treatment: 40 mg/day (20 mg twice daily) to 60 mg/day (once daily or as 30 mg twice daily); Maintenance Treatment: 60 mg/day	120 mg/day
GAD (2.2) Adults	60 mg/day	60 mg/day (once daily)	120 mg/day
DPNP (2.3)	60 mg/day	60 mg/day (once daily)	60 mg/day
Chronic Musculoskeletal Pain (2.5)	30 mg/day	60 mg/day (once daily)	60 mg/day

- Some patients may benefit from starting at 30 mg once daily (2)
- There is no evidence that doses greater than 60 mg/day confers additional benefit, while some adverse reactions were observed to be dose-dependent (2)
- Discontinuing duloxetine delayed-release capsules: Gradually reduce dosage to avoid discontinuation symptoms (2.7, 5.7).
- Hepatic Impairment: Avoid use in patients with chronic liver disease or cirrhosis (5.14)
- Renal Impairment: Avoid use in patients with severe renal impairment, GFR < 30 mL/min (5.14)

----------DOSAGE FORMS AND STRENGTHS----------

20 mg, 30 mg, and 60 mg delayed-release capsules (3)

----------CONTRAINDICATIONS----------

- Serotonin Syndrome and MAOIs: Do not use MAOIs intended to treat psychiatric disorders with duloxetine delayed-release capsules or within 5 days of stopping treatment with duloxetine delayed-release capsules. Do not use duloxetine delayed-release capsules within 14days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start duloxetine delayed-release capsules in a patient who is being treated with linezolid or intravenous methylene blue (4)

----------WARNINGS AND PRECAUTIONS----------

- Hepatotoxicity: Hepatic failure, sometimes fatal, has been reported in patients treated with duloxetine delayed-release capsules. Duloxetine delayed-release capsules 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. Duloxetine delayed-release capsules should not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease (5.2).
- Orthostatic Hypotension, Falls and Syncope: Cases have been reported with duloxetine therapy (5.3).
- Serotonin Syndrome: Serotonin syndrome has been reported with SSRIs and SNRIs, including with duloxetine delayed-release capsules, both when taken alone, but especially when co-administered with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort). If such symptoms occur, discontinue duloxetine delayed-release capsules and initiate supportive treatment. If concomitant use of duloxetine delayed-release capsules with other serotonergic drugs is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases (5.4)
- Abnormal Bleeding: Duloxetine delayed-release capsules may increase the risk of bleeding events. 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 (5.5, 7.4).
- Severe Skin Reactions: Severe skin reactions, including erythema multiforme and Stevens-Johnson Syndrome (SJS), can occur with duloxetine delayed-release capsules. Discontinue duloxetine delayed-release capsules at the first appearance of blisters, peeling rash, mucosal erosions, or any other sign of hypersensitivity if no other etiology can be identified. (5.6)
- Discontinuation: May result in symptoms, including dizziness, headache, nausea, diarrhea, paresthesia, irritability, vomiting, insomnia, anxiety, hyperhidrosis, and fatigue (5.7).
- Activation of mania or hypomania has occurred (5.8).
- Angle-Closure Glaucoma: Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants. (5.9)
- Seizures: Prescribe with care in patients with a history of seizure disorder (5.10).
- Blood Pressure: Monitor blood pressure prior to initiating treatment and periodically throughout treatment (5.11).
- Inhibitors of CYP1A2 or Thioridazine: Should not administer with duloxetine delayed-release capsules (5.12).
- Hyponatremia: Cases of hyponatremia have been reported (5.13).
- Glucose Control in Diabetes: In diabetic peripheral neuropathic pain patients, small increases in fasting blood glucose, and HbA_{1c} have been observed (5.14).
- Conditions that Slow Gastric Emptying: Use cautiously in these patients (5.14).
- Urinary Hesitation and Retention (5.15).

----------ADVERSE REACTIONS----------

- Most common adverse reactions (≥ 5% and at least twice the incidence of placebo patients): nausea, dry mouth, somnolence, constipation, decreased appetite, and hyperhidrosis (6.3).

To report SUSPECTED ADVERSE REACTIONS, contact Hetero Labs Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Potent inhibitors of CYP1A2 should be avoided (7.1).
- Potent inhibitors of CYP2D6 may increase duloxetine concentrations (7.2).
- Duloxetine is a moderate inhibitor of CYP2D6 (7.9).

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data may cause fetal harm (8.1)
- Nursing Mothers: Exercise caution when administered to a nursing woman (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide

Pediatric use information for patients ages 7 to 17 years is approved for Eli Lilly and Company, Inc.'s CYMBALTA® (duloxetine) delayed-release capsules. However, due to Eli Lilly and Company, Inc.'s marketing exclusivity rights, this drug product is not labeled with that pediatric information.

Revised: 05/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

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 *[see Warnings and Precautions (5.1)]*.

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 *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

Duloxetine delayed-release capsules, USP are indicated for the treatment of:

- Major Depressive Disorder *[see Clinical Studies (14.1)]*
- Generalized Anxiety Disorder *[see Clinical Studies (14.2)]*
- Diabetic Peripheral Neuropathy *[see Clinical Studies (14.3)]*
- Chronic Musculoskeletal Pain *[see Clinical Studies (14.5)]*

2 DOSAGE AND ADMINISTRATION

Swallow duloxetine delayed-release capsules whole. Do not chew or crush. Do not open the capsule and sprinkle its contents on food or mix with liquids. All of these might affect the enteric coating. Duloxetine delayed-release capsules can be given without regard to meals. If a dose of duloxetine delayed-release capsules is missed, take the missed dose as soon as it is remembered. If it is almost time for the next dose, skip the missed dose and take the next dose at the regular time. Do not take two doses of duloxetine delayed-release capsules at the same time.

2.1 Dosage for Treatment of Major Depressive Disorder

Administer duloxetine delayed-release capsules 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 *[see Clinical Studies (14.1)]*.

2.2 Dosage for Treatment of Generalized Anxiety Disorder

Adults — For most patients, initiate duloxetine delayed-release capsules 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 *[see Clinical Studies (14.2)]*.

Pediatric use information for patients ages 7 to 17 years is approved for Eli Lilly and Company, Inc.'s CYMBALTA® (duloxetine) delayed-release capsules. However, due to Eli Lilly and Company, Inc.'s marketing exclusivity rights, this drug product is not labeled with that pediatric information.

2.3 Dosage for Treatment of Diabetic Peripheral Neuropathic Pain

Administer duloxetine delayed-release capsules 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 *[see Clinical Studies (14.3)]*. 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 *[see Dosage and Administration (2.6), Use in Specific Populations (8.10), and Clinical Pharmacology (12.3)]*.

2.5 Dosage for Treatment of Chronic Musculoskeletal Pain

Administer duloxetine delayed-release capsules 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 *[see Clinical Studies (14.5)]*.

2.6 Dosing in Special Populations

Hepatic Impairment — Avoid use in patients with chronic liver disease or cirrhosis *[see Warnings and Precautions (5.14) and Use in Specific Populations (8.9)]*.

Severe Renal Impairment — Avoid use in patients with severe renal impairment, GFR < 30 mL/min *[see Warnings and Precautions (5.14) and Use in Specific Populations (8.10)]*.

2.7 Discontinuing Duloxetine Delayed-Release Capsules

Adverse reactions after discontinuation of duloxetine delayed-release capsules, after abrupt or tapered discontinuation, include: dizziness, headache, nausea, diarrhea, paresthesia, irritability, vomiting, insomnia, anxiety, hyperhidrosis, and fatigue. A gradual reduction in dosage rather than abrupt cessation is recommended whenever possible *[see Warnings and Precautions (5.7)]*.

2.8 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 duloxetine delayed-release capsules. Conversely, at least 5 days should be allowed after stopping duloxetine delayed-release capsules before starting an MAOI intended to treat psychiatric disorders *[see Contraindications (4)]*.

2.9 Use of Duloxetine Delayed-Release Capsules with Other MAOIs such as Linezolid or Methylene Blue

Do not start duloxetine delayed-release capsules in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered *[see Contraindications (4)]*.

In some cases, a patient already receiving duloxetine delayed-release capsules therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, duloxetine delayed-release capsules should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 5 days or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with duloxetine delayed-release capsules may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue *[see Warnings and Precautions (5.4)]*.

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with duloxetine delayed-release capsules is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use *[see Warnings and Precautions (5.4)]*.

3 DOSAGE FORMS AND STRENGTHS

Duloxetine Hydrochloride, USP is available as delayed-release capsules

20 mg are Opaque green cap/Opaque green body size '4' hard gelatin capsule imprinted with 'H' on cap and '190' on body, filled with off white colored pellets.

30 mg are Opaque blue cap/ Opaque white body size '3' hard gelatin capsule imprinted with 'H' on cap and '191' on body, filled with off white colored pellets.

60 mg Opaque blue cap/ Opaque green body size '1' hard gelatin capsule imprinted with 'H' on cap and '192' on body, filled with off white colored pellets.

4 CONTRAINDICATIONS

Monoamine Oxidase Inhibitors (MAOIs) — The use of MAOIs intended to treat psychiatric disorders with duloxetine delayed-release capsules or within 5 days of stopping treatment with duloxetine delayed-release capsules is contraindicated because of an increased risk of serotonin syndrome. The use of duloxetine delayed-release capsules within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated *[see Dosage and Administration (2.8) and Warnings and Precautions (5.4)]*.

Starting duloxetine delayed-release capsules 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 *[see Dosage and Administration (2.9) and Warnings and Precautions (5.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 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. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk of differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 Patients Treated
	Increases Compared to Placebo
< 18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥ 65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

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. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

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 *[see Dosage and Administration (2.7) and Warnings and Precautions (5.7) for descriptions of the risks of discontinuation of duloxetine delayed-release capsules]*.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, 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 duloxetine delayed-release capsules should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder — A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that duloxetine delayed-release capsules are not approved for use in treating bipolar depression.

5.2 Hepatotoxicity

There have been reports of hepatic failure, sometimes fatal, in patients treated with duloxetine delayed-release capsules. These cases have presented as hepatitis with abdominal pain, hepatomegaly, and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Duloxetine delayed-release capsules 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.

Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported. Other postmarketing reports indicate that elevated transaminases, bilirubin, and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis.

Duloxetine delayed-release capsules increased the risk of elevation of serum transaminase levels in development program clinical trials. Liver transaminase elevations resulted in the discontinuation of 0.3% (92/34,756) of duloxetine delayed-release capsules-treated patients. In most patients, the median time to detection of the transaminase elevation was about two months. In adult placebo-controlled trials in any indication, for patients with normal and abnormal baseline ALT values, elevation of ALT > 3 times the upper limit of normal occurred in 1.25% (144/11,496) of duloxetine delayed-release capsules-treated patients compared to 0.45% (39/8,716) of placebo-treated patients. In adult placebo-controlled studies using a fixed dose design, there was evidence of a dose response relationship for ALT and AST elevation of > 3 times the upper limit of normal and > 5 times the upper limit of normal, respectively.

Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, duloxetine delayed-release capsules should not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

5.3 Orthostatic Hypotension, Falls and Syncope

Orthostatic hypotension, falls 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 falling appears to be related to the degree of orthostatic decrease in blood pressure as well as other factors that may increase the underlying risk of falls.

In an analysis of patients from all placebo-controlled trials, patients treated with duloxetine delayed-release capsules reported a higher rate of falls compared to patients treated with placebo. Risk appears to be related to the presence of orthostatic decrease in blood pressure. The risk of blood pressure decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as antihypertensives) or are potent CYP1A2 inhibitors *[see Warnings and Precautions (5.12) and Drug Interactions (7.1)]* and in patients taking duloxetine at doses above 60 mg daily. Consideration should be given to dose reduction or discontinuation of duloxetine in patients who experience symptomatic orthostatic hypotension, falls and/or syncope during duloxetine therapy.

Risk of falling also appeared to be proportional to a patient's underlying risk for falls and appeared to increase steadily with age. As elderly patients tend to have a higher underlying risk for falls due to a higher prevalence of risk factors such as use of multiple medications, medical comorbidities and gait disturbances, the impact of increasing age by itself is unclear. Falls with serious consequences including bone fractures and hospitalizations have been reported *[see Adverse Reactions (6.10) and Patient Counseling Information (17)]*.

5.4 Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including duloxetine delayed-release capsules, alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of duloxetine delayed-release capsules with MAOIs intended to treat psychiatric disorders is contraindicated. Duloxetine delayed-release capsules should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking duloxetine delayed-release capsules. Duloxetine delayed-release capsules should be discontinued before initiating treatment with the MAOI *[see Dosage and Administration (2.8, 2.9), and Contraindications (4)]*.

If concomitant use of duloxetine delayed-release capsules with other serotonergic drugs including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases. Treatment with duloxetine delayed-release capsules and any concomitant serotonergic agents, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

5.5 Abnormal Bleeding

SSRIs and SNRIs, including duloxetine, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anti-coagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

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.

5.6 Severe Skin Reactions

Severe skin reactions, including erythema multiforme and Stevens-Johnson Syndrome (SJS), can occur with duloxetine delayed-release capsules. The reporting rate of SJS associated with duloxetine delayed-release capsules use exceeds the general population background incidence rate for this serious skin reaction (1 to 2 cases per million person years). The reporting rate is generally accepted to be an underestimate due to underreporting.

Duloxetine delayed-release capsules 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.

5.7 Discontinuation of Treatment with Duloxetine Delayed-release Capsules

Discontinuation symptoms have been systematically evaluated in patients taking duloxetine. Following abrupt or tapered discontinuation in adult 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, headache, nausea, diarrhea, paresthesia, irritability, vomiting, insomnia, anxiety, hyperhidrosis, and fatigue.

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 duloxetine delayed-release capsules. 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 *[see Dosage and Administration (2.7)]*.

5.8 Activation of Mania/Hypomania

In adult placebo-controlled trials in patients with major depressive disorder, activation of mania or hypomania was reported in 0.1% (4/3,779) of duloxetine-treated patients and 0.04% (1/2,536) of placebo-treated patients. No activation of mania or hypomania was reported in DPNP, GAD, or chronic musculoskeletal pain placebo-controlled trials. 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, duloxetine delayed-release capsules should be used cautiously in patients with a history of mania.

5.9 Angle-Closure Glaucoma

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

5.10 Seizures

Duloxetine has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. In adult placebo-controlled clinical trials, seizures/convulsions occurred in 0.02% (3/12,722) of patients treated with duloxetine and 0.01% (1/9,513) of patients treated with placebo. Duloxetine delayed-release capsules should be prescribed with care in patients with a history of a seizure disorder.

5.11 Effect on Blood Pressure

In adult 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 0.3 mm Hg diastolic in placebo-treated patients. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. In a clinical pharmacology study designed to evaluate the effects of duloxetine on various parameters, including blood pressure at supratherapeutic doses with an accelerated dose titration, there was evidence of increases in supine blood pressure at doses up to 200 mg twice daily. At the highest 200 mg twice daily dose, the increase in mean pulse rate was 5 to 6.8 beats and increases in mean blood pressure were 4.7 to 6.8 mm Hg (systolic) and 4.5 to 7 mm Hg (diastolic) up to 12 hours after dosing.

Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment *[see Adverse Reactions (6.7)]*.

5.12 Clinically Important Drug Interactions

Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Potential for Other Drugs to Affect Duloxetine Delayed-Release Capsules

CYP1A2 Inhibitors — Co-administration of duloxetine delayed-release capsules with potent CYP1A2 inhibitors should be avoided *[see Drug Interactions (7.1)]*.

CYP2D6 Inhibitors — Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 would be expected to, and does, result in higher concentrations (on average of 60%) of duloxetine *[see Drug Interactions (7.2)]*.

Potential for Duloxetine Delayed-Release Capsules to Affect Other Drugs

Drugs Metabolized by CYP2D6 — Co-administration of duloxetine delayed-release capsules 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), phenothiazines and Type 1C antiarrhythmics (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 duloxetine delayed-release capsules. Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, duloxetine delayed-release capsules and thioridazine should not be co-administered *[see Drug Interactions (7.9)]*.

Other Clinically Important Drug Interactions

Alcohol — Use of duloxetine delayed-release capsules concomitantly with heavy alcohol intake may be associated with severe liver injury. For this reason, duloxetine delayed-release capsules should not be prescribed for patients with substantial alcohol use *[see Warnings and Precautions (5.2) and Drug Interactions (7.15)]*.

CNS Acting Drugs — Given the primary CNS effects of duloxetine delayed-release capsules, 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 *[see Warnings and Precautions (5.12) and Drug Interactions (7.16)]*.

5.13 Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including duloxetine delayed-release capsules. 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 duloxetine delayed-release capsules were discontinued. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk *[see Use in Specific Populations (8.5)]*. Discontinuation of duloxetine delayed-release capsules 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.

5.14 Use in Patients with Concomitant Illness

Clinical experience with duloxetine delayed-release capsules in patients with concomitant systemic illnesses is limited. There is no information on the effect that alterations in gastric motility may have on the stability of duloxetine delayed-release capsule's enteric coating. In extremely acidic conditions, duloxetine delayed-release capsules, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using duloxetine delayed-release capsules in patients with conditions that may slow gastric emptying (e.g., some diabetics).

Duloxetine delayed-release capsules have not been systematically evaluated in patients with a recent history of myocardial infarction or unstable coronary artery disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing.

Hepatic Impairment — Avoid use in patients with chronic liver disease or cirrhosis *[see Dosage and Administration (2.6), Warnings and Precautions (5.2), and Use in Specific Populations (8.9)]*.

Severe Renal Impairment — Avoid use in patients with severe renal impairment, GFR < 30 mL/min. Increased plasma concentration of duloxetine, and especially of its metabolites, occur in patients with end-stage renal disease (requiring dialysis) *[see Dosage and Administration (2.6) and Use in Specific Populations (8.10)]*.

Glycemic Control in Patients with Diabetes — As observed in DPNP trials, duloxetine delayed-release capsules treatment worsens glycemic control in some patients with diabetes. In three clinical trials of duloxetine delayed-release capsules 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 A_{1c} (HbA_{1c}) was 7.8%. In the 12-week acute treatment phase of these studies, duloxetine delayed-release capsules were associated with a small increase in mean fasting blood glucose as compared to placebo. In the extension phase of these studies, which lasted up to 52 weeks, mean fasting blood glucose increased by 12 mg/dL in the duloxetine delayed-release capsules group and decreased by 11.5 mg/dL in the routine care group. HbA_{1c} increased by 0.5% in the duloxetine delayed-release capsules and by 0.2% in the routine care groups.

5.15 Urinary Hesitation and Retention

Duloxetine delayed-release capsules are in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during treatment with duloxetine delayed-release capsules, 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.

5.16 Laboratory Tests

No specific laboratory tests are recommended.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in the labeling:

- Suicidal Thoughts and Behaviors in Children, Adolescents and Young Adults *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Hepatotoxicity *[see Warnings and Precautions (5.2)]*
- Orthostatic Hypotension, Falls and Syncope *[see Warnings and Precautions (5.3)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.4)]*
- Abnormal Bleeding *[see Warnings and Precautions (5.5)]*
- Severe Skin Reactions *[see Warnings and Precautions (5.6)]*
- Discontinuation of Treatment with duloxetine delayed-release capsules *[see Warnings and Precautions (5.7)]*
- Activation of Mania/Hypomania *[see Warnings and Precautions (5.8)]*
- Angle-Closure Glaucoma *[see Warnings and Precautions (5.9)]*
- Seizures *[see Warnings and Precautions (5.10)]*
- Effect on Blood Pressure *[see Warnings and Precautions (5.11)]*
- Clinically Important Drug Interactions *[see Warnings and Precautions (5.12)]*
- Hyponatremia *[see Warnings and Precautions (5.13)]*
- Urinary Hesitation and Retention *[see Warnings and Precautions (5.15)]*

6.1 Clinical Trial Data Sources

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. Reactions reported during the studies were not necessarily caused by the therapy, and the frequencies do not reflect investigator impression (assessment) of causality.

Children and Adolescents — The data described below reflect exposure to duloxetine delayed-release capsules in pediatric, 10-week, placebo-controlled trials for MDD (N=341). The population studied (N=476) was 7 to 17 years of age with 42.4% children age 7 to 11 years of age, 50.6% female, and 68.6% white. Patients received 30 to 120 mg per day during placebo-controlled acute treatment studies. Additional data come from the overall total of 822 pediatric patients (age 7 to 17 years of age) with 41.7% children age 7 to 11 years of age and 51.8% female exposed to duloxetine delayed-release capsules in MDD clinical trials up to 36-weeks in length, in which most patients received 30 to 120 mg per day.

Pediatric use information for patients ages 7 to 17 years is approved for Eli Lilly and Company, Inc.'s CYMBALTA® (duloxetine) delayed-release capsules. However, due to Eli Lilly and Company, Inc.'s marketing exclusivity rights, this drug product is not labeled with that pediatric information.

6.2 Adverse Reactions Reported as Reasons for Discontinuation of Treatment in Adult Placebo-Controlled Trials

Major Depressive Disorder — Approximately 8.4% (319/3,779) of the patients who received duloxetine in placebo-controlled trials for MDD discontinued treatment due to an adverse reaction, compared with 4.6% (117/2,536) of the patients receiving placebo. Nausea (duloxetine 1.1%, placebo 0.4%) was the only common adverse reaction reported as a reason for discontinuation and considered to be drug-related (i.e., discontinuation occurring in at least 1% of the duloxetine-treated patients and at a rate of at least twice that of placebo).

Generalized Anxiety Disorder — Approximately 13.7% (139/1,018) of the patients who received duloxetine in placebo-controlled trials for GAD discontinued treatment due to an adverse reaction, compared with 5% (38/767) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 3.3%, placebo 0.4%), and dizziness (duloxetine 1.3%, placebo 0.4%).

Diabetic Peripheral Neuropathic Pain — Approximately 12.9% (117/906) of the patients who received duloxetine in placebo-controlled trials for DPNP discontinued treatment due to an adverse reaction, compared with 5.1% (23/448) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 3.5%, placebo 0.7%), dizziness (duloxetine 1.2%, placebo 0.4%), and somnolence (duloxetine 1.1%, placebo 0%).

Chronic Pain due to Osteoarthritis — Approximately 15.7% (79/503) of the patients who received duloxetine delayed-release capsules in13-week, placebo-controlled trials for chronic pain due to OA discontinued treatment due to an adverse reaction, compared with 7.3% (37/508) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 2.2%, placebo 1%).

Chronic Low Back Pain — Approximately 16.5% (99/600) of the patients who received duloxetine delayed-release capsules in 13-week, placebo-controlled trials for CLBP discontinued treatment due to an adverse reaction, compared with 6.3% (28/441) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine delayed-release capsules 3%, placebo 0.7%), and somnolence (duloxetine delayed-release capsules 1%, placebo 0%).

6.3 Most Common Adult Adverse Reactions

Pooled Trials for all Approved Indications — The most commonly observed adverse reactions in duloxetine-treated patients (incidence of at least 5% and at least twice the incidence in placebo patients) were nausea, dry mouth, somnolence, fatigue, constipation, decreased appetite, and hyperhidrosis.

Diabetic Peripheral Neuropathic Pain — The most commonly observed adverse reactions in duloxetine-treated patients (as defined above) were nausea, somnolence, decreased appetite, constipation, hyperhidrosis, and dry mouth.

Chronic Pain due to Osteoarthritis — The most commonly observed adverse reactions in duloxetine-treated patients (as defined above) were nausea, fatigue, constipation, dry mouth, insomnia, somnolence, and dizziness.

Chronic Low Back Pain — The most commonly observed adverse reactions in duloxetine-treated patients (as defined above) were nausea, dry mouth, insomnia, somnolence, constipation, dizziness, and fatigue.

6.4 Adverse Reactions Occurring at an Incidence of 5% or More Among Duloxetine-Treated Patients in Adult Placebo-Controlled Trials

Table 2 gives the incidence of treatment-emergent adverse reactions in placebo-controlled trials for approved indications that occurred in 5% or more of patients treated with duloxetine and with an incidence greater than placebo.

Table 2: Treatment-Emergent Adverse Reactions: Incidence of 5% or More and Greater than Placebo inPlacebo-Controlled Trials of Approved Indications[a]

Adverse Reaction	Percentage of Patients Reporting Reaction: Duloxetine Delayed-Release Capsules (N=8,100)	Placebo (N=5,655)
Nausea[c]	23	8
Headache	14	12
Dry mouth	13	5
Somnolence[e]	10	3
Fatigue[b,c]	9	5
Insomnia[d]	9	5
Constipation[c]	9	4
Dizziness[c]	9	5
Diarrhea	9	6
Decreased appetite[c]	7	2
Hyperhidrosis[c]	6	1
Abdominal pain[f]	5	4

[a] The inclusion of an event in the table is determined based on the percentages before rounding; however, the percentages displayed in the table are rounded to the nearest integer.
[b] Also includes asthenia
[c] Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies which did not have a placebo lead-in period or dose titration.
[d] Also includes initial insomnia, middle insomnia, and early morning awakening.
[e] Also includes hypersomnia and sedation.
[f] Also includes abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, and gastrointestinal pain.

6.5 Adverse Reactions Occurring at an Incidence of 2% or More Among Duloxetine-Treated Patients in Adult Placebo-Controlled Trials

Pooled MDD and GAD Trials — Table 3 gives the incidence of treatment-emergent adverse reactions in MDD and GAD placebo-controlled trials for approved indications that occurred in 2% or more of patients treated with duloxetine and with an incidence greater than placebo.

Table 3: Treatment-Emergent Adverse Reactions: Incidence of 2% or More in MDD and GAD Placebo-Controlled Trials[a]

System Organ Class / Adverse Reaction	Percentage of Patients Reporting Reaction: Duloxetine Delayed-Release Capsules (N=4,797)	Placebo (N=3,303)
Cardiac Disorders		
Palpitations	2	1
Eye Disorders		
Vision blurred	3	1
Gastrointestinal Disorders		
Nausea[c]	23	8
Dry mouth	14	6
Constipation[c]	9	6
Diarrhea	9	4
Abdominal pain[d]	5	4
Vomiting	4	2
General Disorders and Administration Site Conditions		
Fatigue[e]	9	5
Metabolism and Nutrition Disorders		
Decreased appetite[e]	6	2
Nervous System Disorders		
Headache	14	14
Dizziness[c]	9	5
Somnolencef	9	3
Tremor	3	1
Psychiatric Disorders		
Insomnia[g]	9	5
Agitation[h]	4	2
Anxiety	3	2
Reproductive System and Breast Disorders		
Erectile dysfunction	4	1
Ejaculation delayed[c]	2	1
Ejaculation disorder[i]	3	
Orgasm abnormal[j]	2	< 1
Respiratory, Thoracic, and Mediastinal Disorders		
Yawning	2	< 1
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	6	2

[a] The inclusion of an event in the table is determined based on the percentages before rounding; however, the percentages displayed in the table are rounded to the nearest integer.
[c] Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies which did not have a placebo lead-in period or dose titration.
[d] Also includes abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominaldiscomfort, and gastrointestinal pain
[e] Also includes asthenia
[f] Also includes hypersomnia and sedation
[g] Also includes initial insomnia, middle insomnia, and early morning awakening
[h] Also includes feeling jittery, nervousness, restlessness, tension, and psychomotor hyperactivity
[i] Also includes loss of libido
[j] Also includes anorgasmia

DPNP, another indication, OA, and CLBP — Table 4 gives the incidence of treatment-emergent adverse events that occurred in 2% or more of patients treated with duloxetine delayed-release capsules (determined prior to rounding) in the premarketing acute phase of DPNP, another indication, OA, and CLBP placebo-controlled trials and with an incidence greater than placebo.

Table 4: Treatment-Emergent Adverse Reactions: Incidence of 2% or More and Greater than Placebo in DPNP, another indication, OA, and CLBP Placebo-Controlled Trials[a]

System Organ Class / Adverse Reaction	Percentage of Patients Reporting Reaction: Duloxetine Delayed-Release Capsules (N=3,303)	Placebo (N=2,352)
Gastrointestinal Disorders		
Nausea	23	7
Dry Mouth[b]	11	3
Constipation[b]	10	3
Diarrhea	9	5
Abdominal Pain[c]	5	4
Vomiting	3	2
Dyspepsia	2	1
General Disorders and Administration Site Conditions		
Fatigue[d]	11	5
Infections and Infestations		
Nasopharyngitis	4	4
Upper Respiratory Tract Infection	3	3
Influenza	2	2
Metabolism and Nutrition Disorders		
Decreased Appetite[b]	8	1
Musculoskeletal and Connective Tissue		
Musculoskeletal Pain[e]	3	3
Muscle Spasms	2	2
Nervous System Disorders		
Headache	13	8
Somnolence[b,f]	11	3
Dizziness	9	5
Paraesthesia[g]	2	2
Tremor[b]	2	< 1
Psychiatric Disorders		
Insomnia[b,h]	10	5
Agitation[i]	3	1
Reproductive System and Breast Disorders		
Erectile Dysfunction[b]	4	< 1
Ejaculation Disorder[j]	2	< 1
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	2	2
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	6	1
Vascular Disorders		
Flushing[k]	3	1
Blood pressure increased[l]	2	1

[a] The inclusion of an event in the table is determined based on the percentages before rounding; however, the percentages displayed in the table are rounded to the nearest integer.
[b] Incidence of 120 mg/day is significantly greater than the incidence for 60 mg/day.
[c] Also includes abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness and gastrointestinal pain
[d] Also includes asthenia
[e] Also includes myalgia and neck pain
[f] Also includes hypersomnia and sedation
[g] Also includes hypoesthesia, hypoesthesia facial, genital hypoesthesia and paresthesia oral
[h] Also includes initial insomnia middle insomnia, and early morning awakening
[i] Also includes feeling jittery, nervousness, restlessness, tension and psychomotor hyperactivity
[j] Also includes ejaculation failure
[k] Also includes hot flush
[l] Also includes blood pressure diastolic increased, blood pressure systolic increased, diastolic hypertension, essential hypertension, hypertension, hypertensive crisis, labile hypertension, orthostatic hypertension, secondary hypertension, and systolic hypertension

6.6 Effects on Male and Female Sexual Function in Adults

Changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of psychiatric disorders or diabetes, but they may also be a consequence of pharmacologic treatment. Because adverse sexual reactions are presumed to be voluntarily underreported, the Arizona Sexual Experience Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in 4 MDD placebo-controlled trials. In these trials, as shown in Table 5 below, patients treated with duloxetine hydrochloride delayed-release capsules experienced significantly more sexual dysfunction, as measured by the total score on the ASEX, than did patients treated with placebo. Gender analysis showed that this difference occurred only in males. Males treated with duloxetine hydrochloride delayed-release capsules experienced more difficulty with ability to reach orgasm (ASEX Item 4) than males treated with placebo. Females did not experience more sexual dysfunction on duloxetine hydrochloride delayed-release capsules than on placebo as measured by ASEX total score. Negative numbers signify an improvement from a baseline level of dysfunction, which is commonly seen in depressed patients. Physicians should routinely inquire about possible sexual side effects.

Table 5: Mean Change in ASEX Scores by Gender in MDD Placebo-Controlled Trials

	Male Patients[a]: Duloxetine Delayed-Release Capsules (n=175)	Male Patients[a]: Placebo (n=83)	Female Patients[a]: Duloxetine Delayed-Release Capsules (n=241)	Female Patients[a]: Placebo (n=126)
ASEX Total (Items 1-5)	0.56[b]	-1.07	-1.15	-1.07
Item 1 — Sex drive	-0.07	-0.12	-0.32	-0.24
Item 2 — Arousal	0.01	-0.26	-0.21	-0.18
Item 3 — Ability to achieve erection (men); Lubrication (women)	0.03	-0.25	-0.17	-0.18
Item 4 — Ease of reaching orgasm	0.40c	-0.24	-0.09	-0.13
Item 5 — Orgasm satisfaction	0.09	-0.13	-0.11	-0.17

[a] n=Number of patients with non-missing change score for ASEX total
[b] p=0.013 versus placebo
p< 0.001 versus placebo

6.7 Vital Sign Changes in Adults

In placebo-controlled clinical trials across approved indications for change from baseline to endpoint, duloxetine treatment was associated with mean increases of 0.23 mm Hg in systolic blood pressure and 0.73 mm Hg in diastolic blood pressure compared to mean decreases of 1.09 mm Hg systolic and 0.55 mm Hg diastolic in placebo-treated patients. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure *[see Warnings and Precautions (5.3 and 5.11)]*.

Duloxetine treatment, for up to 26 weeks in placebo-controlled trials across approved indications, typically caused a small increase in heart rate for change from baseline to endpoint compared to placebo of up to 1.37 beats per minute (increase of 1.20 beats per minute in duloxetine-treated patients, decrease of 0.17 beats per minute in placebo- treated patients).

6.8 Laboratory Changes in Adults

Duloxetine delayed-release capsules treatment in placebo-controlled clinical trials across approved indications, was associated with small mean increases from baseline to endpoint in ALT, AST, CPK, and alkaline phosphatase; infrequent, modest, transient, abnormal values were observed for these analytes in duloxetine-treated patients when compared with placebo-treated patients *[see Warnings and Precautions (5.2)]*. High bicarbonate, cholesterol, and abnormal (high or low) potassium, were observed more frequently in duloxetine treated patients compared to placebo.

6.9 Electrocardiogram Changes in Adults

The effect of duloxetine 160 mg and 200 mg administered twice daily to steady state was evaluated in a randomized, double-blinded, two-way crossover study in 117 healthy female subjects. No QT interval prolongation was detected. Duloxetine appears to be associated with concentration-dependent but not clinically meaningful QT shortening.

6.10 Other Adverse Reactions Observed During the Premarketing and Postmarketing Clinical Trial Evaluation of Duloxetine in Adults

Following is a list of treatment-emergent adverse reactions reported by patients treated with duloxetine in clinical trials. In clinical trials of all indications, 34,756 patients were treated with duloxetine. Of these, 26.9% (9,337) took duloxetine for at least 6 months, and 12.4% (4,317) for at least one year. The following listing is not intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) which occurred at a rate equal to or less than placebo.

Reactions are categorized by body system according to the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1,000 patients; rare reactions are those occurring in fewer than 1/1,000 patients.

Cardiac Disorders — *Frequent:* palpitations; *Infrequent:* myocardial infarction and tachycardia.

Ear and Labyrinth Disorders — *Frequent:* vertigo; *Infrequent:* ear pain and tinnitus.

Endocrine Disorders — *Infrequent:* hypothyroidism.

Eye Disorders — *Frequent:* vision blurred; *Infrequent:* diplopia, dry eye, and visual impairment.

Gastrointestinal Disorders — *Frequent:* flatulence; *Infrequent:* dysphagia, eructation, gastritis, gastrointestinal hemorrhage, halitosis, and stomatitis; Rare: gastric ulcer.

General Disorders and Administration Site Conditions — *Frequent:* chills/rigors; *Infrequent: falls, feeling abnormal,* feeling hot and/or cold, malaise, and thirst; *Rare:* gait disturbance.

Infections and Infestations — *Infrequent:* gastroenteritis and laryngitis.

Investigations — *Frequent:* weight increased, weight decreased; *Infrequent:* blood cholesterol increased.

Metabolism and Nutrition Disorders — *Infrequent:* dehydration and hyperlipidemia; *Rare:* dyslipidemia.

Musculoskeletal and Connective Tissue Disorders — *Frequent:* musculoskeletal pain; *Infrequent:* muscle tightness and muscle twitching.

Nervous System Disorders — *Frequent:* dysgeusia, lethargy, and paresthesia/hypoesthesia; *Infrequent:* disturbance in attention, dyskinesia, myoclonus, and poor quality sleep; *Rare:* dysarthria.

Psychiatric Disorders — *Frequent:* abnormal dreams and sleep disorder; *Infrequent:* apathy, bruxism, disorientation/confusional state, irritability, mood swings, and suicide attempt; *Rare:* completed suicide.

Renal and Urinary Disorders — *Frequent*: urinary frequency; *Infrequent:* dysuria, micturition urgency, nocturia, polyuria, and urine odor abnormal.

Reproductive System and Breast Disorders — *Frequent:* anorgasmia/orgasm abnormal; *Infrequent:* menopausal symptoms, sexual dysfunction, and testicular pain; *Rare:* menstrual disorder.

Respiratory, Thoracic and Mediastinal Disorders — *Frequent:* yawning, oropharyngeal pain; *Infrequent:* throat tightness.

Skin and Subcutaneous Tissue Disorders — *Frequent:* pruritus; *Infrequent:* cold sweat, dermatitis contact, erythema, increased tendency to bruise, night sweats, and photosensitivity reaction; *Rare:* ecchymosis.

Vascular Disorders — *Frequent:* hot flush; *Infrequent:* flushing, orthostatic hypotension, and peripheral coldness.

6.11 Adverse Reactions Observed in Children and Adolescent Placebo-Controlled Clinical Trials

The adverse drug reaction profile observed in pediatric clinical trials (children and adolescents) was consistent with the adverse drug reaction profile observed in adult clinical trials. The specific adverse drug reactions observed in adult patients can be expected to be observed in pediatric patients (children and adolescents) *[see Adverse Reactions (6.5)]*. The most common (≥ 5% and twice placebo) adverse reactions observed in pediatric clinical trials include: nausea, diarrhea, decreased weight, and dizziness.

Table 6 provides the incidence of treatment-emergent adverse reactions in MDD pediatric placebo-controlled trials that occurred in greater than 2% of patients treated with duloxetine delayed-release capsules and with an incidence greater than placebo.

Table 6: Treatment-Emergent Adverse Reactions: Incidence of 2% or More and Greater than Placebo in three 10-week Pediatric Placebo-Controlled Trials[a]

System Organ Class / Adverse Reaction	Percentage of Patients Reporting Reaction: Duloxetine Delayed-Release Capsules (N=476)	Placebo (N=362)
Gastrointestinal Disorders		
Nausea	18	8
Abdominal Pain[b]	13	10
Vomiting	9	4
Diarrhea	6	3
Dry Mouth	2	1
General Disorders and Administration Site Conditions		
Fatigue[c]	7	5
Investigations		
Decreased Weightd	14	6
Metabolism and Nutrition Disorders		
Decreased Appetite	10	5
Nervous System Disorders		
Headache	18	13
Somnolence[e]	11	6
Dizziness[c]	8	4
Psychiatric Disorders		
Insomnia[f]	7	4
Respiratory, Thoracic, and Mediastinal Disorders		
Oropharyngeal Pain	4	2
Cough	3	1

[a] The inclusion of an event in the table is determined based on the percentages before rounding; however, the percentages displayed in the table are rounded to the nearest integer.
[b] Also includes abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort, and gastrointestinal pain.
[c] Also includes asthenia.
[d] Frequency based on weight measurement meeting potentially clinically significant threshold of ≥ 3.5% weight loss (N=467 Duloxetine delayed-release capsules; N=354 Placebo).
[e] Also includes hypersomnia and sedation.
[f] Also includes initial insomnia, insomnia, middle insomnia, and terminal insomnia.

Other adverse reactions that occurred at an incidence of less than 2% but were reported by more duloxetine treated patients than placebo treated patients and are associated duloxetine treatment: abnormal dreams (including nightmare), anxiety, flushing (including hot flush), hyperhidrosis, palpitations, pulse increased, and tremor.

Medication Guide

Duloxetine Delayed-release Capsules, USP

(doh-LOCKS-ah-teen)

Read this Medication Guide before you start taking duloxetine delayed-release capsules and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

Talk to your healthcare provider about:

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression, other serious mental illnesses, and suicidal thoughts or actions?

1. **Duloxetine delayed-release capsules and other antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, or young adults within the first few months of treatment or when the dose is changed.**
2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts or actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness).
3. **How can I watch for and try to prevent suicidal thoughts and actions?**
   - Pay close attention to any changes in mood, behavior, actions, thoughts, or feelings, especially sudden changes. This is very important when an antidepressant medicine is started or when the dose is changed.
   - Call your healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
     - Keep all follow-up visits with your healthcare provider as scheduled. Call your healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call your healthcare provider right away if you have any of the following symptoms or feelings, especially if they are new, worse, or worry you. In an emergency, call 911.

- attempts to commit suicide
- acting on dangerous impulses
- acting aggressive , being angry or violent
- thoughts about suicide or dying
- new or worse depression
- new or worse anxiety
- panic attacks
- feeling very agitated or restless
- new or worse irritability
- trouble sleeping
- an extreme increase in activity or talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- Never stop an antidepressant medicine without first talking to a healthcare provider. Stopping an antidepressant medicine suddenly can cause other symptoms.
- Antidepressants are medicines used to treat depression and other illnesses. It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients should discuss all treatment choices with your healthcare provider, not just the use of antidepressants.
- Antidepressant medicines have other side effects. Talk to your healthcare provider about the side effects of the medicine prescribed for you or your family member.
- Antidepressant medicines can interact with other medicines. Know all of the medicines that you or your family member takes. Keep a list of all medicines to show your healthcare provider. Do not start new medicines without first checking with your healthcare provider.

What are duloxetine delayed-release capsules?

Duloxetine delayed-release capsule is a prescription medicine used to treat certain type of depression called Major Depressive Disorder (MDD). Duloxetine delayed-release capsule belongs to a class of medicines known as SNRIs (or serotonin-norepinephrine reuptake inhibitors).

Duloxetine delayed-release capsule is also used to treat or manage:

- Generalized Anxiety Disorder (GAD)
- Diabetic Peripheral Neuropathic Pain (DPNP)
- Chronic Musculoskeletal Pain

Who should not take duloxetine delayed-release capsules?

Do NOT take duloxetine delayed-release capsules if you:

- **take a Monoamine Oxidase Inhibitor (MAOI).** Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid or intravenous methylene blue.
  - Do not take an MAOI within 5 days of stopping duloxetine delayed-release capsules unless directed to do so by your healthcare provider.
  - Do not start duloxetine delayed-release capsules if you stopped taking an MAOI in the last 14 days unless directed to do so by your healthcare provider.

People who take duloxetine delayed-release capsules close in time to an MAOI may have a serious problem called Serotonin Syndrome (see "What are the possible side effects of duloxetine delayed-release capsules ?").

What should I tell my healthcare provider before taking duloxetine delayed-release capsules?

Before starting duloxetine delayed-release capsules, tell your healthcare provider if you:

- have heart problems or high blood pressure
- have diabetes (Duloxetine delayed-release capsules treatment makes it harder for some people with diabetes to control their blood sugar)
- have liver problems
- have kidney problems
- have glaucoma
- have or had seizures or convulsions
- have bipolar disorder or mania
- have low sodium levels in your blood
- have delayed stomach emptying
- have or had bleeding problems
- are pregnant or plan to become pregnant. It is not known if duloxetine delayed-release capsules will harm your unborn baby. Talk to your healthcare provider about the benefits and risks of treating depression or other conditions with duloxetine delayed-release capsules during pregnancy.
- are breastfeeding or plan to breastfeed. Duloxetine can pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby while taking duloxetine delayed-release capsules.

Tell your healthcare provider about all the medicines that you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Duloxetine delayed-release capsules and some medicines may interact with each other, may not work as well, or may cause serious side effects.

Especially tell your healthcare provider if you take:

- triptans used to treat migraine headache
- medicines used to treat mood, anxiety, psychotic or thought disorders, including tricyclics, lithium, buspirone, SSRIs, SNRIs or MAOIs
- tramadol and fentanyl
- cimetidine
- the antibiotics ciprofloxacin, enoxacin
- medicine to treat irregular heart rate (like propafenone, flecainide, quinidine)
- theophylline
- the blood thinner warfarin (Coumadin, Jantoven)
- non-steroidal anti-inflammatory drug (NSAID) (like ibuprofen, naproxen or aspirin).
- over-the-counter supplements such as tryptophan or St. John's Wort
- thioridazine (Mellaril). Mellaril together with duloxetine can cause serious heart rhythm problems or sudden death.

Ask your healthcare provider for a list of these medicines if you are not sure.

Do not take duloxetine delayed-release capsules with any other medicine that contain duloxetine.

How should I take duloxetine delayed-release capsules?

- Take duloxetine delayed-release capsules exactly as your healthcare provider tells you to take it. Your healthcare provider may need to change the dose of duloxetine delayed-release capsules until it is the right dose for you.
- Swallow duloxetine delayed-release capsules whole. Do not chew or crush duloxetine delayed-release capsules.
- Do not open the capsule and sprinkle on food or mix with liquids. Opening the capsule may affect how well duloxetine delayed-release capsule works.
- Duloxetine delayed-release capsules may be taken with or without food.
- If you miss a dose of duloxetine delayed-release capsules, take the missed dose as soon as you remember. If it is almost time for the next dose, skip the missed dose and take your next dose at the regular time. Do not take two doses of duloxetine delayed-release capsules at the same time.
- If you take too much duloxetine delayed-release capsules, call your healthcare provider or poison control center at 1-800-222-1222 right away, or get emergency treatment.
- When switching from another antidepressant to duloxetine delayed-release capsules your healthcare provider may want to lower the dose of the initial antidepressant first to potentially avoid side effects.

What should I avoid while taking duloxetine delayed-release capsules?

- Duloxetine delayed-release capsules can cause sleepiness or may affect your ability to make decisions, think clearly, or react quickly. You should not drive, operate heavy machinery, or do other dangerous activities until you know how duloxetine delayed-release capsule affects you.
- Use of duloxetine delayed-release capsules concomitantly with heavy alcohol intake may be associated with severe liver injury. Avoid heavy alcohol use while taking duloxetine delayed-release capsules.

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Discontinuation-emergent symptoms have been reported when stopping duloxetine delayed-release capsules or other medications in this class. Duloxetine delayed-release capsules should be tapered when discontinuing treatment. Patients should be monitored for symptoms that may occur after discontinuation, including dizziness, nausea, headache, irritability, insomnia, and abnormal dreams [*see Dosage and Administration (2.6)*].

Growth Impairment in Children and Adolescents

Duloxetine delayed-release capsules (mean exposure in clinical trials was 282 days) were associated with a slower rate of growth (height and weight) in children and adolescents. Monitor growth during treatment.

Hepatotoxicity

Cases of severe hepatotoxicity, including acute liver failure, have been reported in patients treated with duloxetine. In many cases, patients had symptoms of autoimmune disease at onset of liver dysfunction. Duloxetine delayed-release capsules are not recommended for patients with acute liver disease. Discontinue duloxetine delayed-release capsules in patients who develop jaundice or other evidence of clinically significant liver dysfunction.

Elevations of Serum Phosphokinase

Increases in serum creatine phosphokinase have been observed in patients taking duloxetine. Consider discontinuing duloxetine delayed-release capsules if these increases are severe.

Serotonin Syndrome

Cases of serotonin syndrome have been reported with duloxetine. Discontinue duloxetine delayed-release capsules if serotonin syndrome is suspected.

Activation of Mania or Hypomania

Activation of mania or hypomania has been reported in a small proportion of patients with mood disorders who were treated with duloxetine. Screen patients for bipolar disorder risk factors prior to initiating duloxetine delayed-release capsules.

Angle-Closure Glaucoma

Pupillary dilation can occur following treatment with duloxetine. Angle-closure glaucoma has occurred in patients treated with duloxetine delayed-release capsules. Patients with untreated anatomically narrow angles should be treated with an appropriate laser or surgical intervention before prescribing duloxetine delayed-release capsules.

Urethral Stricture

Urethral stricture has been reported in patients taking duloxetine delayed-release capsules.

Hyponatremia

Hyponatremia may occur as a result of treatment with duloxetine, including cases with serum sodium lower than 110 mmol/L. Hyponatremia may be due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Elderly patients may be at greater risk of developing hyponatremia with duloxetine. Also consider discontinuation of duloxetine delayed-release capsules in patients with symptomatic hyponatremia and institute appropriate medical intervention.

Anaphylactic Reactions

Rare cases of anaphylactic reactions have been reported with duloxetine. Discontinue duloxetine delayed-release capsules if the patient experiences anaphylaxis.

Effects on Blood Pressure

Duloxetine delayed-release capsules can cause elevations of blood pressure. Pre-existing hypertension should be controlled before initiating duloxetine delayed-release capsules. Monitor blood pressure during treatment with duloxetine delayed-release capsules.

Effects on Heart Rate

Increases in heart rate have been observed with duloxetine delayed-release capsules.

Effects on Cholesterol

Increases in cholesterol have been observed with duloxetine delayed-release capsules.

Sexual Dysfunction

Duloxetine delayed-release capsules may cause symptoms of sexual dysfunction in male and female patients. Ask patients about sexual dysfunction before treatment and inquire about changes during treatment.

Hyperglycemia in Patients with Diabetes

Duloxetine delayed-release capsules may increase blood glucose levels in patients with diabetes. Monitor blood glucose levels in patients with diabetes.

Withdrawal Symptoms

Withdrawal symptoms may occur when duloxetine delayed-release capsules are discontinued. Gradually reduce the dose rather than stopping duloxetine delayed-release capsules abruptly.

Suicidal Thoughts and Behaviors

Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adult patients in short-term studies. Closely monitor patients who are started on duloxetine delayed-release capsules for clinical worsening, suicidal thoughts or behaviors, or unusual changes in behavior.

Interference with Cognitive and Motor Performance

Duloxetine delayed-release capsules may impair judgment, thinking, or motor skills. Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that duloxetine delayed-release capsules therapy does not affect their ability to engage in such activities.

Pediatric Use

Pediatric Use — Information for patients ages 7 to 17 years with MDD is approved for Eli Lilly and Company, Inc.'s CYMBALTA® (duloxetine) delayed-release capsules. However, data in Eli Lilly and Company, Inc.'s CYMBALTA® (duloxetine) delayed-release capsules labeling do not establish the safety and effectiveness of duloxetine delayed-release capsules in this pediatric population. The safety and effectiveness of duloxetine delayed-release capsules in pediatric patients with MDD ages 7 to 17 years were established in two 9-week clinical trials in adolescents 13 to 17 years of age with MDD [*see Clinical Studies (14.2)*].

The safety and effectiveness of duloxetine delayed-release capsule have not been established in pediatric patients younger than 7 years of age.

Interference with Psychomotor Performance

Any psychoactive drug may impair judgment, thinking, or motor skills. Although in controlled studies duloxetine has not been shown to impair psychomotor performance, cognitive function, or memory, any drug with CNS activity has the potential to impair these skills. Caution patients about operating hazardous machinery including automobiles, until they are reasonably certain that duloxetine delayed-release capsules therapy does not affect their ability to engage in such activities.

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Figure 1: Kaplan-Meier Estimation of Cumulative Proportion of Patients with Relapse (MDD Study 1)

Figure 2: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity – CLBP-1

Figure 3: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity – OAS-1

Figure 4: Kaplan-Meier Estimates of Sustained Proportion of Patients Responding During the 6-Month Open-Label Extension Period (MDD Study 2)

Figure 5: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity – CLBP-2

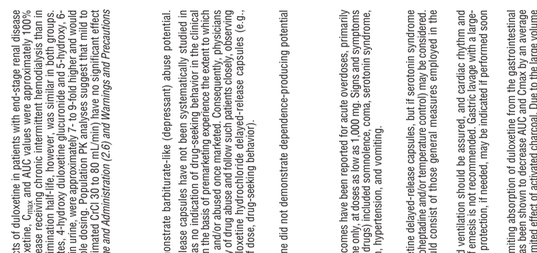


Figure 6: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity – CLBP-1

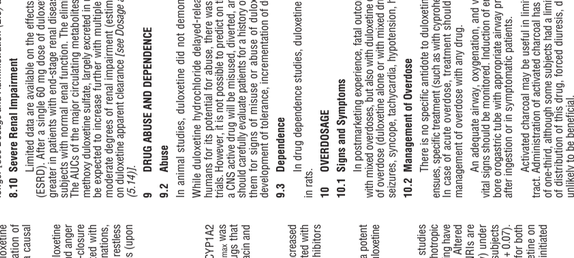
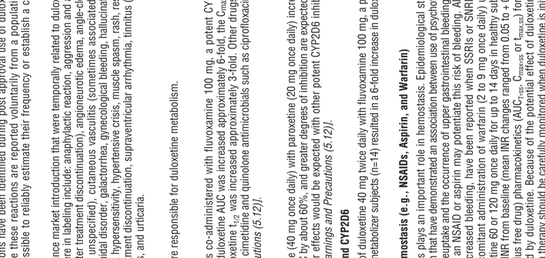


Figure 7: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity – CLBP-1



What are the possible side effects of duloxetine delayed-release capsules?

Duloxetine delayed-release capsules may cause serious side effects, including: See "What is the most important information I should know about duloxetine delayed-release capsules?"

Common possible side effects in people who take duloxetine delayed-release capsules include:

1. **liver damage. Symptoms may include:**
   - itching
   - right upper abdominal pain
   - dark urine
   - yellow skin or eyes
   - enlarged liver
   - increased liver enzymes
2. **changes in blood pressure and falls.** Monitor your blood pressure before starting and throughout treatment. Duloxetine delayed-release capsules may:
   - increase your blood pressure.
   - decrease your blood pressure when standing and cause dizziness or fainting mostly when first starting duloxetine delayed-release capsules or when increasing the dose.
   - increase risk of falls, especially in elderly.
3. **Serotonin Syndrome -This condition can be life-threatening and symptoms may include**:
   - agitation, hallucinations, coma or other changes in mental status
   - coordination problems or muscle twitching (overactive reflexes)
   - racing heartbeat, high or low blood pressure
   - sweating or fever
   - nausea, vomiting, or diarrhea
   - muscle rigidity
   - dizziness
   - flushing
   - tremor
   - seizures
4. **abnormal bleeding**: Duloxetine delayed-release capsules and other antidepressant medicines may increase your risk of bleeding or bruising, especially if you take the blood thinner warfarin (Coumadin, Jantoven), a non-steroidal anti- inflammatory drug (NSAIDs, like ibuprofen or naproxen), or aspirin.
5. **severe skin reactions:** Duloxetine delayed-release capsules may cause serious skin reactions that may require stopping its use. This may need to be treated in a hospital and may be life-threatening. Call your health care provider right away or get emergency help if you have skin blisters, peeling rash, sores in the mouth, hives or any other allergic reactions.
6. **discontinuation symptoms:** Do not stop duloxetine delayed-release capsules without first talking to your healthcare provider. Stopping duloxetine delayed-release capsules too quickly or changing from another antidepressant too quickly may result in serious symptoms including:
   - anxiety
   - irritability
   - feeling tired or problems sleeping
   - headache
   - sweating
   - dizziness
   - electric shock-like sensations
   - vomiting or nausea
   - diarrhea
7. **manic episodes:**
   - greatly increased energy
   - severe trouble sleeping
   - racing thoughts
   - reckless behavior
   - unusually grand ideas
   - excessive happiness or irritability
   - talking more or faster than usual
8. **visual problems:**
   - eye pain
   - changes in vision
   - swelling or redness in or around the eye

   Only some people are at risk for these problems. You may want to undergo an eye examination to see if you are at risk and receive preventative treatment if you are.
9. **seizures or convulsions**
10. **low salt (sodium) levels in the blood.** Elderly people may be at greater risk for this. Symptoms may include:
    - headache
    - weakness or feeling unsteady
    - confusion, problems concentrating or thinking or memory problems
11. **problems with urination. Symptoms may include:**
    - decreased urine flow
    - unable to pass any urine

The most common side effects of duloxetine delayed-release capsules include:

- nausea
- dry mouth
- sleepiness
- fatigue
- constipation
- loss of appetite
- increased sweating
- dizziness

Common possible side effects in children and adolescents who take duloxetine delayed-release capsules include:

- nausea
- decreased weight
- dizziness

Side effects in adults may also occur in children and adolescents who take duloxetine delayed-release capsules. Children and adolescents should have height and weight monitored during treatment.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of duloxetine delayed-release capsules. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to 1-800-FDA-1088.

How should I store duloxetine delayed-release capsules?

Store duloxetine delayed-release capsules at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Keep duloxetine delayed-release capsules and all medicines out of the reach of children.

General information about the safe and effective use of duloxetine delayed-release capsules

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use duloxetine delayed-release capsules for a condition for which it was not prescribed. Do not give duloxetine delayed-release capsules to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about duloxetine delayed-release capsules. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider or pharmacist for information about duloxetine delayed-release capsules that is written for healthcare professionals.

For more information, call 1-866-495-1995.

What are the ingredients in duloxetine delayed-release capsules, USP?

Active ingredient: duloxetine hydrochloride, USP

Inactive ingredients: carboxy methyl ethyl cellulose, crospovidone, FD & C Blue 2, gelatin, hypromellose, isopropyl alcohol, polyethylene glycol, polysorbate 80, povidone, sodium lauryl sulfate, sucrose, sugar spheres, talc and titanium dioxide. In addition, the 20 mg and 60 mg capsules also contain iron oxide yellow.

The imprinting ink contains, butyl alcohol, dehydrated alcohol, isopropyl alcohol, propylene glycol, shellac, and strong ammonia solution. The 20 mg capsule also contains black iron oxide and potassium hydroxide. The 30 mg capsule also contains yellow iron oxide. The 60 mg capsule also contains potassium hydroxide and titanium dioxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration

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Revised: 05/2016