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 thoughts and behavior in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. (5.1)

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

Duloxetine Delayed-Release Capsules are a serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for the treatment of:

- Major depressive disorder (MDD) in adults (1)
- Generalized anxiety disorder (GAD) in adults and pediatric patients 7 years of age and older (1)

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

- Do not initiate treatment with Duloxetine Delayed-Release Capsules. Use another duloxetine delayed-release capsule product for initial dosage, titration, and doses below 80 mg per day. (2.1)
- Administer Duloxetine Delayed-Release Capsules once daily on an empty stomach at least one hour before or two hours after a meal. Swallow whole, do not open, chew or crush. Do not sprinkle the capsule contents on food or mix with liquids. (2.1)
- MDD: Administer Duloxetine Delayed-Release Capsules in doses of 80 mg, 90 mg, or 120 mg. Periodically reassess for appropriate dosing. (2.2)
- GAD: Administer Duloxetine Delayed-Release Capsules in doses of 90 mg or 120 mg. Periodically reassess for appropriate dosing. (2.3)
- The maximum dosage is 120 mg once daily (2.2, 2.3)
- When discontinuing treatment, reduce dose gradually whenever possible to avoid discontinuation symptoms. Gradual dosage reduction will require use of another duloxetine delayed-release capsule product. (2.6)

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

Delayed-release capsules: 80 mg, 90 mg, and 120 mg (3)

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

- Concomitant use of monoamine oxidase inhibitors (MAOIs), or use within 14 days of stopping MAOIs (4)
- 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. Discontinue Duloxetine Delayed-Release Capsules in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established. Avoid use in patients with substantial alcohol use or evidence of chronic liver disease. (5.2)
- Orthostatic Hypotension, Falls and Syncope: Consider dosage reduction or discontinuation if these events occur. (5.3)
- Serotonin Syndrome: Increased risk when co-administered with other serotonergic agents but also when taken alone. If it occurs, discontinue Duloxetine Delayed-Release Capsules and serotonergic agents. (5.4)
- Increased Risk of Bleeding: May increase the risk of bleeding events. Concomitant use of antiplatelet drugs and anticoagulants may increase this risk. (5.5, 7, 8.1)
- Severe Skin Reactions: Severe skin reactions, including erythema multiforme and Stevens-Johnson Syndrome (SJS), can occur. Discontinue 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 Syndrome: Taper dose when possible and monitor for discontinuation symptoms. (5.7)
- Activation of Mania or Hypomania: Prior to initiating, screen patients for personal or family history of bipolar disorder, mania, or hypomania. (5.8)
- 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 Increases: Monitor blood pressure prior to initiating treatment and periodically throughout treatment. (5.11)
- Hyponatremia: Can occur in association with SIADH; consider discontinuation. (5.12)
- Glucose Control in Diabetes: Worsened glycemic control has been observed. (5.13)
- Conditions that Slow Gastric Emptying: Use cautiously in these patients. (5.13)
- Sexual Dysfunction: Duloxetine Delayed-Release Capsules may cause symptoms of sexual dysfunction. (5.15)

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

Most common adverse reactions (≥5% and at least twice the incidence of placebo-treated patients): (6.1)

- Adults: nausea, dry mouth, somnolence, constipation, decreased appetite, and hyperhidrosis
- Pediatric Patients: decreased weight, decreased appetite, nausea, vomiting, fatigue, and diarrhea

To report SUSPECTED ADVERSE REACTIONS, contact Almatica Pharma LLC at 1-877-447-7979 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Strong CYP1A2 inhibitors: Avoid concomitant use. (7.1)
- Potent inhibitors of CYP2D6 may increase Duloxetine Delayed-Release Capsule concentrations. (7.1)
- Duloxetine Delayed-Release Capsule is a moderate inhibitor of CYP2D6. (7.1)

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

- Pregnancy: Third trimester use may increase risk for symptoms of poor adaptation (respiratory distress, temperature instability, feeding difficulty, hypotonia, tremor, irritability) in the neonate. (8.1)
- Hepatic Impairment: Avoid use in patients with chronic liver disease or cirrhosis. (8.6)
- Renal Impairment: Avoid use in patients with severe renal impairment, GFR <30 mL/minute. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2026

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FULL PRESCRIBING INFORMATION

WARNING: 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 all antidepressant-treated patients for clinical worsening, and emergence of suicidal thoughts and behaviors *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

Duloxetine Delayed-Release Capsules are indicated for the treatment of:

- Major depressive disorder in adults
- Generalized anxiety disorder in adults and pediatric patients 7 years of age and older

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

Do not initiate treatment with Duloxetine Delayed-Release Capsules 80 mg, 90 mg, and 120 mg. Use another duloxetine delayed-release capsule product for initial dosage, titration, and doses below 80 mg per day. Refer to the Prescribing Information of other duloxetine delayed-release capsule products for the recommended dosage of those products.

Administer Duloxetine Delayed-Release Capsules orally once daily on an empty stomach at least one hour before or two hours after a meal *[see Pharmacokinetics (12.3)]*. Swallow whole and do not chew or crush. Do not open the delayed-release capsule and sprinkle its contents on food or mix with liquids because these actions might affect the enteric coating. 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.

2.2 Dosage for Treatment of Major Depressive Disorder

Administer Duloxetine Delayed-Release Capsules in adults with MDD receiving at least 60 mg per day of another duloxetine delayed-release capsule product for one week *[see Dosage and Administration (2.1), Clinical Studies (14.1)]*. While duloxetine at a 120 mg per day dose was shown to be effective, there is no evidence that doses greater than 60 mg per day confer any additional benefits.

Administer Duloxetine Delayed-Release Capsules once daily in doses of 80 mg, 90 mg, or 120 mg, titrating dose as tolerated when appropriate. Periodically reassess patients to determine the need for maintenance treatment and the appropriate dosage for such treatment.

The maximum studied dosage is 120 mg once daily.

2.3 Dosage for Treatment of Generalized Anxiety Disorder

Adults Less than 65 Years of Age with GAD

Administer Duloxetine Delayed-Release Capsules in adults less than 65 years of age with GAD receiving at least 60 mg once daily of another duloxetine delayed-release capsule product for one week *[see Dosage and Administration (2.1), Clinical Studies (14.2)]*. While duloxetine at a 120 mg once daily dosage was shown to be effective, there is no evidence that doses greater than 60 mg per day confer additional benefit. Nevertheless, if a decision is made to increase the dosage beyond 60 mg once daily, increase dosage in increments of 30 mg once daily.

Administer Duloxetine Delayed-Release Capsules once daily in doses of 90 mg or 120 mg. Periodically reassess patients to determine the need for maintenance treatment and the appropriate dosage for such treatment.

The maximum studied dosage is 120 mg once daily.

Geriatric Patients with GAD

Administer Duloxetine Delayed-Release Capsules in geriatric patients with GAD receiving at least 60 mg once daily of another duloxetine delayed-release capsule product for two weeks *[see Dosage and Administration (2.1), Clinical Studies (14.2)]*. Patients may benefit from duloxetine dosages above 60 mg once daily. If a decision is made to increase the dosage beyond 60 mg once daily, increase dosage in increments of 30 mg once daily.

Administer Duloxetine Delayed-Release Capsules once daily in doses of 90 mg or 120 mg. Periodically reassess patients to determine the need for maintenance treatment and the appropriate dosage for such treatment.

The maximum studied dosage is 120 mg once daily.

Pediatric Patients 7 to 17 years of Age with GAD

Administer Duloxetine Delayed-Release Capsules in pediatric patients 7 to 17 years of age with GAD receiving at least 60 mg once daily of another duloxetine delayed-release capsule product for two weeks *[see Dosage and Administration (2.1), Clinical Studies (14.2)]*. Some patients may benefit from duloxetine dosages above 60 mg once daily. If a decision is made to increase the dosage beyond 60 mg once daily, increase dosage in increments of 30 mg once daily.

Administer Duloxetine Delayed-Release Capsules once daily in doses of 90 mg or 120 mg. Periodically reassess patients to determine the need for maintenance treatment and the appropriate dosage for such treatment.

The maximum studied dosage is 120 mg once daily.

2.4 Dosage in Patients with Hepatic Impairment or Severe Renal Impairment

Avoid use in patients with chronic liver disease or cirrhosis *[see Warnings and Precautions (5.13) and Use in Specific Populations (8.6)]*.

Recommended dosage in patients with mild to moderate renal impairment (estimated creatinine clearance (CrCl) 30-80 mL/min; CrCl was estimated using Cockcroft-Gault method) is similar to that in patients with normal renal function. Avoid use in patients with severe renal impairment, estimated CrCl < 30 mL/minute *[see Warnings and Precautions (5.13) and Use in Specific Populations (8.7)]*.

2.5 Screen for Bipolar Disorder Prior to Starting Duloxetine Delayed-Release Capsules

Prior to initiating treatment with Duloxetine Delayed-Release Capsules, screen patients for a personal or family history of bipolar disorder, mania, or hypomania *[see Warnings and Precautions (5.8)]*.

2.6 Discontinuing Duloxetine Delayed-Release Capsules

Adverse reactions may occur upon discontinuation of 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 the dose, rather than abrupt cessation, is recommended whenever possible *[see Warnings and Precautions (5.7)]*.

Given that Duloxetine Delayed-Release Capsules are not available in strengths below 80 mg, gradual dosage reduction will require the use of another duloxetine delayed-release capsule product *[see Dosage and Administration (2.1)]*.

2.7 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 another duloxetine delayed-release capsule product. Duloxetine Delayed-Release Capsules may be initiated after titration with another duloxetine delayed-release product. Conversely, at least 5 days should be allowed after stopping Duloxetine Delayed-Release Capsules (or another duloxetine delayed-release capsule) before starting an MAOI intended to treat psychiatric disorders *[see Contraindications (4)]*.

2.8 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 Delayed-Release Capsules are available as:

80 mg: Hard shell gelatin capsules, with "ALM" printed axially on the opaque pale yellow cap and "821" printed axially on the opaque white body. Each capsule contains 89.8 mg of duloxetine hydrochloride, USP equivalent to 80 mg duloxetine.

90 mg: Hard shell gelatin capsules, with "ALM" printed axially on the opaque green cap and "913" printed axially on the opaque white body. Each capsule contains 101 mg of duloxetine hydrochloride, USP equivalent to 90 mg duloxetine.

120 mg: Hard shell gelatin capsules, with "ALM" printed axially on the opaque light green cap and "791" printed axially on the opaque white body. Each capsule contains 134.7 mg of duloxetine hydrochloride, USP equivalent to 120 mg duloxetine.

4 CONTRAINDICATIONS

Duloxetine Delayed-Release Capsules are contraindicated in patients

- who are using or within 14 days of stopping an MAOI intended to treat psychiatric disorders because of an increased risk of serotonin syndrome. Allow at least 5 days after stopping Duloxetine Delayed-Release Capsules prior to initiation of an MAOI to treat psychiatric disorders. *[see Dosage and Administration (2.7), Warnings and Precautions (5.4)]*.
- who are using other MAOIs such as linezolid or intravenous methylene blue because of an increased risk of serotonin syndrome *[see Dosage and Administration (2.8), Warnings and Precautions (5.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Thoughts and Behaviors in Pediatric and Young Adult Patients

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in the antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was

an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in MDD. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 1.

Table 1: Risk Differences of the Number of Patients of Suicidal Thoughts and Behavior in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric and Adult Patients

Age Range	Drug-Placebo Difference in Number of Patients of Suicidal Thoughts or Behaviors per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional patients
18 to 24	5 additional patients
	Decreases Compared to Placebo
25 to 64	1 fewer patient
≥65	6 fewer patients

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with MDD that antidepressants delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors.

Monitor all antidepressant-treated patients for any indication for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy, and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing Duloxetine Delayed-Release Capsules, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

5.2 Hepatotoxicity

There have been reports of hepatic failure, sometimes fatal, in patients treated with duloxetine. 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 (ULN) 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 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-treated patients. In most patients, the median time to detection of the transaminase elevation was about two months. In adult placebo-controlled trials, for patients with normal and abnormal baseline ALT values, elevation of ALT >3 times the ULN occurred in 1.25% (144/11,496) of duloxetine-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 duloxetine dose response relationship for ALT and AST elevation of >3 times the ULN and >5 times the ULN, respectively.

Because it is possible that Duloxetine Delayed-Release Capsules and alcohol may interact to cause liver injury or that Duloxetine Delayed-Release Capsules 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 in patients treated with recommended duloxetine dosages. Syncope and orthostatic hypotension tend to occur within the first week of therapy but can occur at any time during Duloxetine Delayed-Release Capsules treatment, particularly after dose increases. The risk of falling appears to be related to the degree of orthostatic decrease in blood pressure (BP) 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 reported a higher rate of falls compared to patients treated with placebo. Risk appears to be related to the presence of orthostatic decrease in BP. The risk of BP decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as antihypertensives) or are potent CYP1A2 inhibitors *[see Drug Interactions (7.1)]* and in patients taking duloxetine delayed-release capsules at doses above 60 mg daily. Consideration should be given to dose reduction or discontinuation of Duloxetine Delayed-Release Capsules in patients who experience symptomatic orthostatic hypotension, falls and/or syncope during Duloxetine Delayed-Release Capsules 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 geriatric 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 fractures and hospitalizations have been reported with use of duloxetine delayed-release capsules *[see Adverse Reactions (6.1)]*.

5.4 Serotonin Syndrome

Serotonin-norepinephrine reuptake inhibitors (SNRIs), including Duloxetine Delayed-Release Capsules, can precipitate serotonin syndrome, a potentially life-threatening condition. The risk is increased with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, meperidine, methadone, tryptophan, buspirone, amphetamines, and St. John's Wort) and with drugs that impair metabolism of serotonin, i.e., MAOIs, *[see Contraindications (4), Drug Interactions (7.1)]*. Serotonin syndrome can also occur when these drugs are used alone.

Serotonin syndrome signs and 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 gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of Duloxetine Delayed-Release Capsules with MAOIs is contraindicated. In addition, do not initiate Duloxetine Delayed-Release Capsules in a patient being treated with MAOIs such as linezolid or intravenous methylene blue. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection). If it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking Duloxetine Delayed-Release Capsules, discontinue Duloxetine Delayed-Release Capsules before initiating treatment with the MAOI *[see Contraindications (4), Drug Interactions (7.1)]*.

Monitor all patients taking Duloxetine Delayed-Release Capsules for the emergence of serotonin syndrome. Discontinue treatment with Duloxetine Delayed-Release Capsules and any concomitant serotonergic agents immediately if the above symptoms occur, and initiate supportive symptomatic treatment. If concomitant use of Duloxetine Delayed-Release Capsules with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome and monitor for symptoms.

5.5 Increased Risk of Bleeding

Drugs that interfere with serotonin reuptake inhibition, including Duloxetine Delayed-Release Capsules, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), 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. A post-marketing study showed a higher incidence of postpartum hemorrhage in mothers taking duloxetine. Other bleeding events related to SSRI and SNRI use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Inform patients about the increased risk of bleeding associated with the concomitant use of Duloxetine Delayed-Release Capsules and NSAIDs, aspirin, or other drugs that affect coagulation *[see Drug Interactions (7.1)]*.

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 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 Syndrome

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.

Monitor patients 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 healthcare provider may continue decreasing the dose but at a more gradual rate. Given that Duloxetine Delayed-Release Capsules are not available in strengths below 80 mg, gradual dosage reduction will require the use of another duloxetine delayed-release capsule product *[see Dosage and Administration (2.1, 2.6)]*.

5.8 Activation of Mania/Hypomania

In controlled clinical trials in adult patients with major depressive disorder, symptoms of mania or hypomania were reported in 0.1% of patients treated with duloxetine. No activation of mania or hypomania was reported in placebo-controlled trials for other indications. 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. Avoid use of antidepressants, including Duloxetine Delayed-Release Capsules, in patients with anatomically narrow angles.

5.10 Seizures

Duloxetine Delayed-Release Capsules 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% (1/9513) 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 Increases in Blood Pressure

In adult placebo-controlled clinical trials across the approved adult populations 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.

Monitor blood pressure before initiating treatment with Duloxetine Delayed-Release Capsules and periodically during treatment *[see Adverse Reactions (6.1)]*. Pre-existing hypertension should be controlled before initiating treatment with Duloxetine Delayed-Release Capsules. Caution should be exercised in treating patients with pre-existing hypertension, cardiovascular, or cerebrovascular conditions that might be compromised by increases in blood pressure. For patients who experience sustained increase in blood pressure while receiving Duloxetine Delayed-Release Capsules, discontinuation or other appropriate medical intervention should be considered.

Given that Duloxetine Delayed-Release Capsules are not available in strengths below 80 mg, gradual dosage reduction will require the use of another duloxetine delayed-release capsule product.

5.12 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 with duloxetine use and appeared to be reversible when duloxetine was discontinued. Geriatric 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.

5.13 Use in Patients with Concomitant Illness

Clinical experience with duloxetine 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 Capsules' enteric coating. In extremely acidic conditions, duloxetine, 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 Warnings and Precautions (5.2), Use in Specific Populations (8.6)]*.

Severe Renal Impairment

Avoid use in patients with severe renal impairment, GFR <30 mL/minute. Increased plasma concentration of duloxetine, and especially of its metabolites, occur in patients with end-stage renal disease (requiring dialysis) *[see Use in Specific Populations (8.7)]*.

Glycemic Control in Patients with Diabetes

As observed in trials for another indication, duloxetine treatment worsened glycemic control in some patients with diabetes.

5.14 Urinary Hesitation and Retention

Duloxetine Delayed-Release Capsules is 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.

5.15 Sexual Dysfunction

Use of SNRIs, including Duloxetine Delayed-Release Capsules, may cause symptoms of sexual dysfunction *[see Adverse Reactions (6.1)]*. In male patients, SNRI use may result in ejaculatory delay or failure, decreased libido, and erectile dysfunction. In female patients, SNRI use may result in decreased libido and delayed or absent orgasm.

It is important for prescribers to inquire about sexual function prior to initiation of Duloxetine Delayed-Release Capsules and to inquire specifically about changes in sexual function during treatment, because sexual function may not be spontaneously reported. When evaluating changes in sexual function, obtaining a detailed history (including timing of symptom onset) is important because sexual symptoms may have other causes, including the underlying psychiatric disorder. Discuss potential management strategies to support patients in making informed decisions about treatment.

6 ADVERSE REACTIONS

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

- Suicidal Thoughts and Behaviors in Pediatric and Young Adult Patients *[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)]*
- Increased Risk of Bleeding *[see Warnings and Precautions (5.5)]*
- Severe Skin Reactions *[see Warnings and Precautions (5.6)]*
- Discontinuation Syndrome *[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)]*
- Increases in Blood Pressure *[see Warnings and Precautions (5.11)]*
- Hyponatremia *[see Warnings and Precautions (5.12)]*
- Urinary Hesitation and Retention *[see Warnings and Precautions (5.14)]*
- Sexual Dysfunction *[see Warnings and Precautions (5.15)]*

6.1 Clinical Trials Experience

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 safety of Duloxetine Delayed-Release Capsules for the treatment for major depressive disorder (MDD) in adults and for the treatment of generalized anxiety disorder (GAD) in adults and pediatric patients is based upon adequate and well-controlled studies of another duloxetine delayed-release capsule product. The results of these adequate and well-controlled studies of duloxetine delayed-release capsules are presented below.

The stated frequencies of adverse reactions represent the proportion of patients who experienced, at least once, one 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.

Adverse Reactions in Adults

Adult Clinical Trial Database

The data described below reflect exposure to duloxetine delayed-release capsules in placebo-controlled trials for MDD (N=3779), GAD (N=1018), and other indications (N=3303). The population studied was 17 years to 89 years of age. 66% and 61% were female, and 82% and 73% were Caucasian in the MDD and GAD populations, respectively. Most patients received duloxetine delayed-release capsules dosages of a total of 60 mg to 120 mg per day *[see Clinical Studies (14.1, 14.2)]*. The data below do not include results of the trial examining the efficacy of duloxetine delayed-release capsules in patients ≥ 65 years old for the treatment of generalized anxiety disorder; however, the adverse reactions observed in this geriatric sample were generally similar to adverse reactions in the overall adult population.

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

Major Depressive Disorder

Approximately 8.4% (319/3779) of the duloxetine delayed-release capsules-treated patients in placebo-controlled adult trials for MDD discontinued treatment due to an adverse reaction, compared with 4.6% (117/2536) of placebo-treated patients. Nausea (duloxetine delayed-release capsules 1.1%, placebo 0.4%) was the only 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 delayed-release capsules-treated patients and at a rate of at least twice that of placebo-treated patients).

Generalized Anxiety Disorder

Approximately 13.7% (139/1018) of the duloxetine delayed-release capsules-treated patients in placebo-controlled adult trials for GAD discontinued treatment due to an adverse reaction, compared with 5% (38/767) for placebo-treated patients. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine delayed-release capsules 3.3%, placebo 0.4%), and dizziness (duloxetine delayed-release capsules 1.3%, placebo 0.4%).

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

The most commonly observed adverse reactions in duloxetine delayed-release capsule-treated patients (incidence of at least 5% and at least twice the incidence in placebo patients) were nausea, dry mouth, somnolence, constipation, decreased appetite, and hyperhidrosis.

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

Table 2: Adverse Reactions: Incidence of 5% or More and Greater than Placebo in Placebo-Controlled Trials of Approved Adult Populations[a]

Adverse Reaction	Percentage of Patients Reporting Reaction	
	Another Duloxetine Product (N=8100)	Placebo (N=5655)
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] Includes adults with MDD, GAD, and other indications. 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.

Adverse Reactions in Pooled MDD and GAD Trials in Adults

Table 3 displays the incidence of adverse reactions in MDD and GAD placebo-controlled trials that occurred in 2% or more of patients treated with duloxetine delayed-release capsules and with an incidence greater than placebo-treated patients.

Table 3: Adverse Reactions: Incidence of 2% or More and Greater than Placebo in MDD and GAD Placebo-Controlled Trials in Adults[a,b]

System Organ Class / Adverse Reaction	Percentage of Patients Reporting Reaction	
	Another Duloxetine Product (N=4797)	Placebo (N=3303)
Cardiac Disorders		
Palpitations	2	1
Eye Disorders		
Vision blurred	3	1
Gastrointestinal Disorders		
Nausea[c]	23	8
Dry mouth	14	6
Constipation[c]	9	4
Diarrhea	9	6
Abdominal pain[d]	5	4
Vomiting	4	2
General Disorders and Administration Site Conditions		
Fatigue[e]	9	5
Metabolism and Nutrition Disorders		
Decreased appetite[c]	6	2
Nervous System Disorders		
Headache	14	14
Dizziness[c]	9	5
Somnolence[f]	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
Libido decreased[i]	3	1
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.

[b] For GAD, there were no adverse reactions that were significantly different between treatments in adults ≥65 years that were also not significant in the adults <65 years.

[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] Includes abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort, and gastrointestinal pain.

[e] Includes asthenia.

[f] Includes hypersomnia and sedation.

[g] Includes initial insomnia, middle insomnia, and early morning awakening.

[h] Includes feeling jittery, nervousness, restlessness, tension and psychomotor hyperactivity.

[i] Includes loss of libido.

[j] Includes anorgasmia.

Effects on Male and Female Sexual Function in Adults with MDD

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 adverse reactions, was used prospectively in 4 MDD placebo-controlled adult trials *[see Clinical Studies (14.1)]*. The ASEX scale includes five questions that pertain to the following aspects of sexual function: 1) sex drive, 2) ease of arousal, 3) ability to achieve erection (men) or lubrication (women), 4) ease of reaching orgasm, and 5) orgasm satisfaction. Positive numbers signify a worsening of sexual function from baseline. Negative numbers signify an improvement from a baseline level of dysfunction, which is commonly seen in depressed patients.

In these trials, male patients treated with duloxetine delayed-release capsules experienced significantly more sexual dysfunction, as measured by the total score on the ASEX and the ability to reach orgasm, than placebo-treated male patients (see Table 4). Female patients treated with duloxetine delayed-release capsules did not experience more sexual dysfunction than placebo-treated female patients as measured by ASEX total score. Healthcare providers should routinely inquire about possible sexual adverse reactions in duloxetine delayed-release capsules-treated patients.

Table 4: Mean Change in ASEX Scores by Gender in MDD Placebo-Controlled Adult Trials

	Male Patients[a]		**Female Patients[a]**	
	Another Duloxetine Product (n=175)	**Placebo (n=83)**	**Another Duloxetine Product (n=241)**	**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	0.40[c]	-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.

[c] p<0.001 versus placebo.

Vital Sign Changes in Adults

In placebo-controlled clinical trials across approved adult populations for change from baseline to endpoint, duloxetine delayed-release capsules-treated patients had mean increases of 0.23 mm Hg in systolic blood pressure (SBP) and 0.73 mm Hg in diastolic blood pressure (DBP) compared to mean decreases of 1.09 mm Hg in SBP and 0.55 mm Hg in DBP 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, 5.11)]*.

Duloxetine delayed-release capsules treatment, for up to 26 weeks in placebo-controlled trials across approved adult populations, 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 delayed-release capsules-treated patients, decrease of 0.17 beats per minute in placebo-treated patients).

Laboratory Changes in Adults

Duloxetine delayed-release capsules treatment in placebo-controlled clinical trials across approved adult populations, 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 delayed-release capsules-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 delayed-release capsules-treated patients compared to placebo-treated patients.

Other Adverse Reactions Observed During the Clinical Trial Evaluation of Duloxetine Delayed-Release Capsules in Adults

Following is a list of adverse reactions reported by patients treated with duloxetine delayed-release capsules in clinical adult trials. In clinical trials of all approved adult populations, 34,756 patients were treated with duloxetine delayed-release capsules. Of these, 27% (9337) took duloxetine delayed-release capsules for at least 6 months, and 12% (4317) took duloxetine delayed-release capsules 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 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients.

- Cardiac Disorders - *Frequent:* palpitations; *Infrequent:* myocardial infarction, tachycardia, and Takotsubo cardiomyopathy.
- 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 paraesthesia/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.

Adverse Reactions Observed in Placebo-Controlled Clinical Trials in Pediatric Patients

Pediatric Clinical Trial Database

The data described below reflect exposure to duloxetine delayed-release capsules (N=567) in pediatric patients 7 to 18 years of age from 10-week, placebo-controlled trials for MDD (N=341) and GAD (N=135), and a 13-week trial for another indication (N=91). Duloxetine Delayed-Release Capsules are not approved for the treatment of MDD in pediatric patients *[see Use in Specific Populations (8.4)]*. Of the duloxetine delayed-release capsules-treated patients in these studies, 36% were 7 to 11 years of age (64% were between 12 to 18 years old), 55% were female, and 69% were Caucasian. Patients received 30 mg to 120 mg duloxetine delayed-release capsules per day during placebo-controlled acute treatment studies. In the trials up to 40 weeks long, there were 988 duloxetine delayed-release capsules-treated pediatric patients aged 7 to 17 years of age (most patients received 30 mg to 120 mg per day) – 35% were 7 to 11 years of age (65% were 12 to 17 years old) and 56% were female.

Most Common Adverse Reactions in Pediatric Trials

The most common adverse reactions (≥5% in duloxetine delayed-release capsules-treated patients and at least twice the incidence of placebo-treated patients) in all pooled pediatric populations (MDD, GAD, and another indication) were decreased weight, decreased appetite, nausea, vomiting, fatigue, and diarrhea.

Adverse Reactions in Pediatric Patients Aged 7 to 17 Years Old with MDD and GAD

The adverse reaction profile observed in clinical trials in pediatric patients aged 7 years to 18 years old with MDD and GAD was consistent with the adverse reaction profile observed in adult clinical trials. The most common (≥5% and twice placebo) adverse reactions observed in these pediatric clinical trials included: nausea, diarrhea, decreased weight, and dizziness.

Table 5 provides the incidence of adverse reactions in MDD and GAD pediatric placebo-controlled trials that occurred in greater than 2% of patients treated with duloxetine delayed-release capsules and with an incidence greater than patients treated with placebo. Duloxetine Delayed-Release Capsules are not approved in the treatment of MDD in pediatric patients *[see Use in Specific Populations (8.4)]*.

Table 5: Adverse Reactions: Incidence of 2% or More and Greater than Placebo in Three 10-week Pediatric Placebo-Controlled Trials in MDD and GAD[a]

System Organ Class/Adverse Reaction	Percentage of Pediatric Patients Reporting Reaction	
	Another Duloxetine Product (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 Weight[d]	14	6
Metabolism and Nutrition Disorders		
Decreased Appetite	10	5
Nervous System Disorders		
Headache	18	13
Somnolence[e]	11	6
Dizziness	8	4
Psychiatric Disorders		
Insomnia[f]	7	4
Respiratory, Thoracic, and Mediastinal Disorders		
Oropharyngeal Pain	4	2
Cough	3	1

[a] Duloxetine Delayed-Release Capsules are not approved for the treatment of pediatric MDD *[see Use in Specific Populations (8.4)]*. 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 greater than or equal to 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% and were reported by more duloxetine delayed-release capsules-treated patients than placebo-treated patients in pediatric MDD and GAD clinical trials included: abnormal dreams (including nightmare), anxiety, flushing (including hot flush), hyperhidrosis, palpitations, pulse increased, and tremor (Duloxetine Delayed-Release Capsules are not approved to treat pediatric patients with MDD).

The most commonly reported symptoms following discontinuation of duloxetine delayed-release capsules in pediatric MDD and GAD clinical trials included headache, dizziness, insomnia, and abdominal pain *[see Warnings and Precautions (5.7)]*.

Growth (Height and Weight) in Pediatric Patients 7 to 17 Years Old with GAD and MDD

Decreased appetite and weight loss have been observed in association with the use of SSRIs and SNRIs. Duloxetine delayed-release capsules-treated pediatric patients in clinical trials experienced a 0.1 kg mean decrease in weight at 10 weeks, compared with a mean weight gain of approximately 0.9 kg in placebo-treated pediatric patients. The proportion of patients who experienced a clinically significant decrease in weight (≥3.5%) was greater in the duloxetine delayed-release capsules group than in the placebo group (16% and 6%, respectively). Subsequently, over the 4- to 6-month uncontrolled extension periods, duloxetine delayed-release capsules-treated patients on average trended toward recovery to their expected baseline weight percentile based on population data from age- and sex-matched peers.

In studies up to 9 months, duloxetine delayed-release capsules-treated pediatric patients experienced an increase in height of 1.7 cm on average (2.2 cm increase in patients 7 to 11 years of age and 1.3 cm increase in patients 12 to 17 years of age). While height increase was observed during these studies, a mean decrease of 1% in height percentile was observed (decrease of 2% in patients 7 to 11 years of age and increase of 0.3% in patients 12 to 17 years of age). Weight and height should be monitored regularly in pediatric patients treated with duloxetine delayed-release capsules *[see Use in Specific Populations (8.4)]*.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of duloxetine delayed-release capsules. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions reported since market introduction that were temporally related to duloxetine therapy and not mentioned elsewhere in labeling include: acute pancreatitis, anaphylactic reaction, aggression and anger (particularly early in treatment or after treatment discontinuation), angioneurotic edema, angle-closure glaucoma, colitis (microscopic or unspecified), cutaneous vasculitis (sometimes associated with systemic involvement), extrapyramidal disorder, galactorrhea, gynecological bleeding, hallucinations, hyperglycemia, hyperprolactinemia, hypersensitivity, hypertensive crisis, muscle spasm, rash, restless legs syndrome, seizures upon treatment discontinuation, supraventricular arrhythmia, tinnitus (upon treatment discontinuation), trismus, and urticaria.

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with Duloxetine Delayed-Release Capsules

Table 6: Clinically Significant Drug Interactions with Duloxetine Delayed-Release Capsules

Monoamine Oxidase Inhibitors (MAOIs)	
Prevention or Management	Concomitant use of Duloxetine Delayed-Release Capsules is contraindicated in patients taking MAOIs, including MAOIs such as linezolid or intravenous methylene blue *[see Dosage and Administration (2.7, 2.8), Contraindications (4), Warnings and Precautions (5.4)]*.

Mechanism and Clinical Effect(s)	Concomitant use of SSRIs and SNRIs, including Duloxetine Delayed-Release Capsules, with MAOIs increases the risk of serotonin syndrome.
Other Serotonergic Drugs	
Prevention or Management	Monitor for symptoms of serotonin syndrome when Duloxetine Delayed-Release Capsules is used concomitantly with other drugs that may affect the serotonergic neurotransmitter systems. If serotonin syndrome occurs, consider discontinuation of Duloxetine Delayed-Release Capsules and/or concomitant serotonergic drugs *[see Dosage and Administration (2.6), Warnings and Precautions (5.4)]*.
Mechanism and Clinical Effect(s)	Concomitant use of Duloxetine Delayed-Release Capsules with other serotonergic drugs increases the risk of serotonin syndrome.
Alcohol	
Prevention or Management	Avoid use in patients with chronic liver disease or heavy alcohol use *[see Warnings and Precautions (5.2)]*.
Mechanism and Clinical Effect(s)	Concomitant use of Duloxetine Delayed-Release Capsules and alcohol may cause liver injury or aggravate pre-existing liver disease.
Drugs that Interfere with Hemostasis	
Prevention or Management	Closely monitor for bleeding for patients receiving an antiplatelet or anticoagulant drug when Duloxetine Delayed-Release Capsules are initiated or discontinued *[Warnings and Precaution (5.5)]*.
Mechanism and Clinical Effect(s)	Concomitant use of Duloxetine Delayed-Release Capsules with an antiplatelet or anticoagulant drug may potentiate the risk of bleeding.
Strong CYP1A2 Inhibitors	
Prevention or Management	Avoid concomitant use of Duloxetine Delayed-Release Capsules with strong CYP1A2 inhibitors *[see Clinical Pharmacology (12.3)].*
Mechanism and Clinical Effect(s)	Concomitant use of Duloxetine Delayed-Release Capsules with CYP1A2 inhibitors increase the exposures of duloxetine.
Strong CYP2D6 Inhibitors	
Prevention or Management	Monitor for adverse events and adjust the dose of Duloxetine Delayed-Release Capsules as clinically appropriate when co-administering with strong CYP2D6 inhibitors *[see Clinical Pharmacology (12.3)].*
Mechanism and Clinical Effect(s)	Concomitant use of Duloxetine Delayed-Release Capsules with CYP2D6 inhibitors increase the exposures of duloxetine. Greater degrees of inhibition are expected with higher doses of CYP2D6 inhibitors.
CYP2D6 Poor Metabolizers Using Strong Inhibitor of CYP1A2	
Prevention or Management	Avoid co-administration of Duloxetine Delayed-Release Capsules and strong CYP1A2 inhibitors in patients who are CYP2D6 poor metabolizers *[see Clinical Pharmacology (12.3)]*.
Mechanism and Clinical Effect(s)	Concomitant administration of Duloxetine Delayed-Release Capsules with strong CYP1A2 inhibitors in patients who are CYP2D6 poor metabolizers results in increased duloxetine exposures.

Drugs Metabolized by CYP2D6	
Prevention or Management	Monitor plasma concentrations of CYP2D6 substrate and reduce dosage of CYP2D6 substrate drug if necessary *[see Clinical Pharmacology (12.3)]*.
Mechanism and Clinical Effect(s)	Concomitant use of duloxetine increases exposures of a drug primarily metabolized by CYP2D6 which may increase the risk of toxicity of the CYP2D6 substrate drug.
Drugs Metabolized by CYP1A2	
Prevention or Management	Monitor for adverse events and adjust the dose of Duloxetine Delayed-Release Capsules as clinically appropriate *[see Clinical Pharmacology (12.3)]*.
Mechanism and Clinical Effect(s)	Concomitant use of Duloxetine Delayed-Release Capsules with CYP1A2 substrates may increase the exposures of CYP1A2 substrate.
CNS Drugs	
Prevention or Management	Monitor for adverse events and adjust the dose of Duloxetine Delayed-Release Capsules as clinically appropriate *[see Clinical Pharmacology (12.3)]*.
Mechanism and Clinical Effect(s)	Concomitant use of Duloxetine Delayed-Release Capsules with other centrally acting drugs may increase the CNS effects of duloxetine.
Drugs that Affect Gastric Acidity	
Prevention or Management	Monitor for adverse events and adjust the dose of Duloxetine Delayed-Release Capsules as clinically appropriate *[see Clinical Pharmacology (12.3)]*.
Mechanism and Clinical Effect(s)	In patients with conditions that may slow gastric emptying (e.g., some diabetics) and drugs that raise the gastrointestinal pH may lead to earlier the release of duloxetine.
Drugs Highly Bound to Plasma Protein	
Prevention or Management	Monitor for adverse events and adjust the dose of Duloxetine Delayed-Release Capsules as clinically appropriate *[see Clinical Pharmacology (12.3)]*.
Mechanism and Clinical Effect(s)	Concomitant use of Duloxetine Delayed-Release Capsules with highly protein bound drugs may cause increased free concentrations of the other drug, potentially resulting in adverse reactions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors the pregnancy outcomes in women exposed to antidepressants, including Duloxetine Delayed-Release Capsules, during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or visiting online at https://womensmentalhealth.org/research/pregnancyregistry/antidepressants.

Risk Summary

Data from a postmarketing retrospective cohort study indicate that use of duloxetine in the month before delivery may be associated with an increased risk of postpartum hemorrhage. Data from published literature and from a postmarketing retrospective cohort study have not identified a clear drug-associated risk of major birth defects or

other adverse developmental outcomes *(see Data)*. There are risks associated with untreated depression in pregnancy, and with exposure to SNRIs and SSRIs, including Duloxetine Delayed-Release Capsules, during pregnancy *(see Clinical Considerations).*

In rats and rabbits treated with duloxetine during the period of organogenesis, fetal weights were decreased but there was no evidence of developmental effects at doses up to 3 times and 6 times, respectively, the maximum recommended human dose (MRHD) of 120 mg/day given to adolescents on a mg/m^2 basis. When duloxetine was administered orally to pregnant rats throughout gestation and lactation, pup weights at birth and pup survival to 1 day postpartum were decreased at a dose 2 times the MRHD given to adolescents on a mg/m^2 basis. At this dose, pup behaviors consistent with increased reactivity, such as increased startle response to noise and decreased habituation of locomotor activity were observed. Post-weaning growth was not adversely affected.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated Maternal and/or Embryo/Fetal Risk

Women who discontinue antidepressants during pregnancy are more likely to experience a relapse of major depression than women who continue antidepressants. This finding is from a prospective, longitudinal study that followed 201 pregnant women with a history of major depressive disorder who were euthymic and taking antidepressants at the beginning of pregnancy. Consider the risk of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum.

Maternal Adverse Reactions

Use of Duloxetine Delayed-Release Capsules in the month before delivery may be associated with an increased risk of postpartum hemorrhage *[see Warnings and Precautions (5.5)].*

Fetal/Neonatal Adverse Reaction

Neonates exposed to duloxetine and other SNRIs or SSRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These findings are consistent with either a direct toxic effect of the SNRIs or SSRIs, or possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome *[see Warnings and Precautions (5.4)]*.

Data

Human Data

Data from a postmarketing retrospective claims-based cohort study found an increased risk for postpartum hemorrhage among 955 pregnant women exposed to duloxetine in the last month of pregnancy compared to 4,128,460 unexposed pregnant women (adjusted relative risk: 1.53; 95% CI: 1.08-2.18). The same study did not find a clinically meaningful increase in the risk for major birth defects in the comparison of 2,532 women exposed to duloxetine in the first trimester of pregnancy to 1,284,827 unexposed women after adjusting for several confounders. Methodologic limitations include possible residual confounding, misclassification of exposure and outcomes, lack of direct measures of disease severity, and lack of information about alcohol use, nutrition, and over-the-counter medication exposures.

Animal Data

In animal reproduction studies, duloxetine has been shown to have adverse effects on embryo/fetal and postnatal development.

When duloxetine was administered orally to pregnant rats and rabbits during the period of organogenesis, there was no evidence of malformations or developmental variations at doses up to 45 mg/kg/day [3 times and 6 times, respectively, the MRHD of 120 mg/day given to adolescents on a mg/m^2 basis]. However, fetal weights were decreased at this dose, with a no-effect dose of 10 mg/kg/day (approximately equal to the MRHD in rats and 2 times the MRHD in rabbits).

When duloxetine was administered orally to pregnant rats throughout gestation and lactation, the survival of pups to 1 day postpartum and pup body weights at birth and during the lactation period were decreased at a dose of 30 mg/kg/day (2 times the MRHD given to adolescents on a mg/m^2 basis); the no-effect dose was 10 mg/kg/day. Furthermore, behaviors consistent with increased reactivity, such as increased startle response to noise and decreased habituation of locomotor activity, were observed in pups following maternal exposure to 30 mg/kg/day. Post-weaning growth and reproductive performance of the progeny were not affected adversely by maternal duloxetine treatment.

8.2 Lactation

Risk Summary

Data from published literature report the presence of duloxetine in human milk *(see Data)*. There are reports of sedation, poor feeding, and poor weight gain in infants exposed to duloxetine through breast milk *(see Clinical Considerations)*. There are no data on the effect of duloxetine on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Duloxetine Delayed-Release Capsules and any potential adverse effects on the breastfed child from Duloxetine Delayed-Release Capsules or from the underlying maternal condition.

Clinical Considerations

Infants exposed to Duloxetine Delayed-Release Capsules should be monitored for sedation, poor feeding and poor weight gain.

Data

Disposition of duloxetine was studied in 6 lactating women who were at least 12 weeks postpartum and had elected to wean their infants. The women were given 40 mg of duloxetine delayed-release twice daily for 3.5 days. The peak concentration measured in breast milk occurred at a median of 3 hours after the dose. The amount of duloxetine in breast milk was approximately 7 mcg/day while on that dose; the estimated daily infant dose was approximately 2 mcg/kg/day, which is less than 1% of the maternal dose. The presence of duloxetine metabolites in breast milk was not examined.

8.4 Pediatric Use

Antidepressants increased the risk of suicidal thoughts and behavior in pediatric patients. Monitor all pediatric patients being treated with antidepressants for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of treatment, or at times of dosage changes *[see Warnings and Precautions (5.1)]*. Perform regular monitoring of weight and growth in pediatric patients treated with Duloxetine Delayed-Release Capsules *[see Adverse Reactions (6.1)]*.

Generalized Anxiety Disorder

The safety and effectiveness of Duloxetine Delayed-Release Capsules for the treatment of generalized anxiety disorder (GAD) in patients 7 years to 17 years of age is based upon an adequate and well-controlled study of another duloxetine delayed-release capsule product. Use of Duloxetine Delayed-Release Capsules for this indication is supported by evidence from a single 10-week, placebo-controlled trial (Study 6) in 272 patients aged 7 to 17 years with GAD. Duloxetine delayed-release capsules demonstrated superiority over placebo as measured by greater improvement in the Pediatric Anxiety Rating Scale (PARS) for GAD severity score *[see Clinical Studies (14.2)]*.

The safety and effectiveness of Duloxetine Delayed-Release Capsules for the treatment of GAD have not been established in pediatric patients less than 7 years of age.

Major Depressive Disorder

The safety and effectiveness of Duloxetine Delayed-Release Capsules have not been established in pediatric patients for the treatment of MDD. Effectiveness was not demonstrated in two adequate and well controlled trials conducted in 800 pediatric patients aged 7 years to 17 years with MDD. Neither duloxetine delayed-release capsules nor an active control approved for treatment of pediatric MDD were superior to placebo in the 10-week trials. The most frequently observed adverse reactions in the MDD pediatric 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.

Juvenile Animal Toxicology Data

Duloxetine administration to young rats from post-natal day 21 (weaning) through post-natal day 90 (adult) resulted in decreased body weights that persisted into adulthood, but recovered when drug treatment was discontinued; slightly delayed (~1.5 days) sexual maturation in females, without any effect on fertility; and a delay in learning a complex task in adulthood, which was not observed after drug treatment was discontinued. These effects were observed at the high dose of 45 mg/kg/day (2 times the MRHD, for a child); the no-effect-level was 20 mg/kg/day (≈1 times the MRHD, for a child).

8.5 Geriatric Use

Geriatric Exposure in Premarketing Clinical Trials of Duloxetine

- Of the 2,418 patients in MDD trials, 6% (143) were 65 years of age or over.

In the MDD and GAD studies, no overall differences in safety or effectiveness were generally observed between these patients and younger adult patients, and other reported clinical experience has not identified differences in responses between these geriatric and younger adult patients, but greater sensitivity of some older patients cannot be ruled out.

SSRIs and SNRIs, including Duloxetine Delayed-Release Capsules, have been associated with clinically significant hyponatremia in geriatric patients, who may be at greater risk for this adverse reaction *[see Warnings and Precautions (5.12)]*.

In an analysis of data from all placebo-controlled trials, patients treated with duloxetine reported a higher rate of falls compared to placebo-treated patients. The increased risk appears to be proportional to a patient's underlying risk for falls. Underlying risk appears to increase steadily with age. As geriatric patients tend to have a higher prevalence of risk factors for falls such as medications, medical comorbidities and gait disturbances, the impact of increasing age by itself on falls during duloxetine treatment is unclear. Falls with serious consequences including bone fractures and hospitalizations have been reported with duloxetine use *[see Warnings and Precautions (5.3), Adverse Reactions (6.1)]*.

The pharmacokinetics of duloxetine after a single dose of 40 mg were compared in healthy elderly females (65 years to 77 years) and healthy middle-age females (32 years to 50 years). There was no difference in the C_{max}, but the area under the concentration-time curve (AUC) of duloxetine was somewhat (about 25%) higher and the half-life about 4 hours longer in the elderly females. Population pharmacokinetic analyses suggest that the typical values for clearance decrease by approximately 1% for each year of age between 25 years to 75 years of age; but age as a predictive factor only accounts for a small percentage of between-patient variability. Dosage adjustment based on the age of the adult patient is not necessary.

8.6 Hepatic Impairment

Avoid Duloxetine Delayed-Release Capsules use in patients with chronic liver disease or cirrhosis *[see Warnings and Precautions (5.2)]*.

Patients with clinically evident hepatic impairment have decreased duloxetine metabolism and elimination. After a single 20 mg dose of duloxetine, 6 cirrhotic patients with moderate liver impairment (Child-Pugh Class B) had a mean plasma duloxetine clearance about 15% that of age- and gender-matched healthy subjects, with a 5-fold increase in mean exposure (AUC). Although C_{max} in the cirrhotic patients was similar to healthy subjects, the half-life was about 3 times longer *[see Warnings and Precautions (5.13)]*.

8.7 Renal Impairment

Avoid Duloxetine Delayed-Release Capsules use in patients with severe renal impairment, estimated CrCl <30 mL/minute.

Limited data are available on the effects of duloxetine in patients with end-stage renal disease (ESRD). After a single 60 mg dose of duloxetine, C_{max} and AUC values were approximately 100% greater in patients with ESRD receiving chronic intermittent hemodialysis than in subjects with normal renal function. The elimination half-life, however, was similar in both groups. The AUCs of the major circulating metabolites, 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate, largely excreted in urine, were approximately 7- to 9-fold higher and would be expected to increase further with multiple dosing. Population pharmacokinetic analyses suggest that mild to moderate degrees of renal impairment (estimated CrCl 30-80 mL/min) have no significant effect on duloxetine apparent clearance *[see Warnings and Precautions (5.13)]*.

10 OVERDOSAGE

10.1 Signs and Symptoms

In postmarketing experience, fatal outcomes have been reported for acute duloxetine overdoses, primarily with mixed overdoses, but also with duloxetine only, including 1000 mg of duloxetine (approximately 8.3 times the maximum recommended dosage). Signs and symptoms of overdose (duloxetine alone or with mixed drugs) included somnolence, coma, serotonin syndrome, seizures, syncope, tachycardia, hypotension, hypertension, and vomiting.

10.2 Management of Overdose

There is no specific antidote to a duloxetine overdosage, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered.

In case of acute overdose with Duloxetine Delayed-Release Capsules, treatment should consist of those general measures employed in the management of overdose with any drug, such as assuring an adequate airway, oxygenation, and ventilation and monitoring cardiac rhythm and vital signs. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Induction of emesis is not recommended.

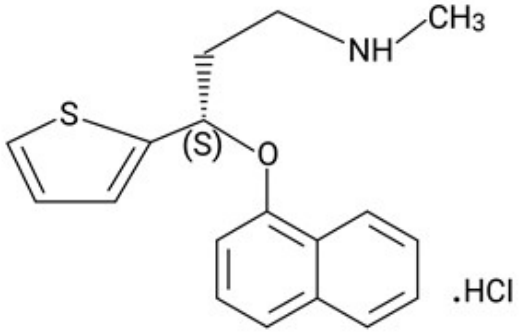
Activated charcoal may be useful in limiting absorption of duloxetine from the gastrointestinal tract. Administration of activated charcoal has been shown to decrease duloxetine AUC and C_{max} by an average of one-third, although some patients had a limited effect of activated charcoal. Due to the large volume of distribution of duloxetine, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be beneficial.

In managing overdose, the possibility of multiple drug involvement should be considered. A specific caution involves patients who overdose with Duloxetine Delayed-Release Capsules and tricyclic antidepressants. In such a case, decreased clearance of the parent tricyclic and/or its active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation *[see Warnings and Precautions (5.4), Drug Interactions (7)]*.

Consider contacting a Poison Help line (1-800-222-1222 or www.poison.org) for additional information on the treatment of overdosage.

11 DESCRIPTION

Duloxetine Delayed-Release Capsules contain duloxetine hydrochloride, a selective serotonin and norepinephrine reuptake inhibitor (SNRI). The chemical name of duloxetine hydrochloride 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:



Duloxetine hydrochloride is a white to brownish-white solid, which is slightly soluble in water.

Duloxetine Delayed-Release Capsules are intended for oral administration. Each capsule contains enteric-coated pellets of 80 mg, 90 mg, or 120 mg of duloxetine (equivalent to 89.8 mg, 101 mg, or 134.7 mg of duloxetine hydrochloride, USP, respectively). These enteric-coated pellets are designed to prevent degradation of the drug in the acidic environment of the stomach. Inactive ingredients of the enteric-coated pellets include colloidal silicon dioxide, cysteine, hypromellose, hypromellose phthalate, sucrose, sugar spheres, talc, and triethyl citrate. The capsule shell ingredients for the 80 mg strength are D&C Yellow #10, gelatin, and titanium dioxide. The capsule shell ingredients for the 90 mg strength are D&C Yellow #10, FD&C Blue #1, FD&C Red #40, gelatin, and titanium dioxide. The capsule shell ingredients for the 120 mg strength are D&C Yellow #10, FD&C Green #3, FD&C Red #40, gelatin, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 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.

12.2 Pharmacodynamics

Preclinical studies have shown that 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).

Duloxetine is in a class of drugs known to affect urethral resistance *[see Warnings and Precautions (5.14)]*.

Cardiac Electrophysiology

The effect of duloxetine 160 mg and 200 mg administered twice daily (2.7 times and 3.3 times the maximum recommended dosage, respectively) to steady state was evaluated in a randomized, double-blinded, two-way crossover study in 117 healthy female adult subjects. No QT interval prolongation was detected. Duloxetine appears to be associated with concentration-dependent but not clinically meaningful QT shortening.

Alcohol

When duloxetine and ethanol were administered several hours apart so that peak concentrations of each would coincide, duloxetine did not increase the impairment of mental and motor skills caused by alcohol.

12.3 Pharmacokinetics

No clinically significant difference in duloxetine exposure was observed following oral administration of either duloxetine delayed-release capsules or Duloxetine Delayed-Release Capsules.

Duloxetine pharmacokinetics are dose proportional over the therapeutic range. Steady-state plasma concentrations are typically achieved after 3 days of dosing.

Absorption

After oral duloxetine delayed-release capsules administration, the median lag time of absorption (T_{lag}) is 2 hours and maximal plasma concentrations (C_{max}) of duloxetine occurs at 6 hours post dose. 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.

Effect of Food

Food delays the median time to reach peak concentration from 6 to 8 hours. Administration of Duloxetine Delayed-Release Capsules to healthy subjects with a high-fat meal (containing 1000 calories, 50% fat) increased C_{max} and area under the plasma concentration-time curve (AUC_{inf}) by 29% and 35%, respectively, compared to the fasted state.

Distribution

The apparent volume of distribution averages about 1640 L. 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.

Elimination

Duloxetine has an elimination half-life of about 12 hours (range 8 hours to 17 hours). Elimination of duloxetine is mainly through hepatic metabolism involving two P450 isozymes, CYP1A2 and CYP2D6.

Metabolism

Biotransformation and disposition of duloxetine in humans have been determined following oral administration of ^{14}C-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 *in vitro*. Metabolites found in plasma include 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate.

Excretion

Many additional metabolites have been identified in urine, some representing only minor pathways of elimination. Only trace (less than 1% of the 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.

Specific Populations

Pediatric Patients

Duloxetine steady-state plasma concentration was comparable in pediatric patients 7 to 17 years of age and adult patients. The average steady-state duloxetine concentration was approximately 30% lower in this pediatric population relative to adult patients. The model-predicted duloxetine steady state plasma concentrations in pediatric patients 7 to 17 years of age were mostly within the concentration range observed in adult patients and did not exceed the concentration range in adults.

Male and Female Patients

Duloxetine's half-life is similar in men and women. Dosage adjustment based on gender is not necessary.

Smoking Status

Duloxetine bioavailability (AUC) appears to be reduced by about one-third in smokers. Dosage modifications are not recommended for smokers.

Race

No specific pharmacokinetic study has been conducted to investigate the effects of race.

Patients with Renal Impairment

Limited data are available on the effects of duloxetine delayed-release capsules in patients with end-stage renal disease (ESRD). After a single 60 mg dose of duloxetine delayed-release capsules, C_{max} and AUC_{inf} values were approximately 100% greater in patients with ESRD receiving chronic intermittent hemodialysis than in subjects with normal renal function. The elimination half-life, however, was similar in both groups. The AUC_{inf} of the major circulating metabolites, 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6 methoxy duloxetine sulfate, largely excreted in urine, were approximately 7-to 9-fold higher and would be expected to increase further with multiple dosing. Population pharmacokinetic analyses suggest that mild to moderate degrees of renal impairment (estimated CrCl 30-80 mL/min; CrCl was estimated using Cockcroft-Gault method) have no significant effect on duloxetine apparent clearance *[see Dosage and Administration (2.4) and Warnings and Precautions (5.13)]*.

Patients with Hepatic Impairment

Patients with clinically evident hepatic impairment have decreased duloxetine metabolism and elimination. After a single 20 mg dose of duloxetine delayed-release capsules, 6 cirrhotic patients with moderate liver impairment (Child-Pugh Class B) had a mean plasma duloxetine clearance about 15% that of age-and gender-matched healthy subjects, with a 5-fold increase in mean exposure (AUC_{inf}). Although C_{max} in the cirrhotic patients was similar to healthy subjects, the half-life was about 3 times longer *[see Dosage and Administration (2.4) and Warnings and Precautions (5.13)]*.

Drug Interaction Studies

Clinical Studies: Effect of other drugs on duloxetine

Fluvoxamine

When duloxetine 60 mg was co-administered with fluvoxamine 100 mg, a strong CYP1A2 inhibitor, to male subjects (n = 14) duloxetine AUC was increased approximately 6 fold, the C_{max} was increased about 2.5 fold, and duloxetine $t_{1/2}$ was increased approximately 3 fold *[see Drug Interactions (7.1)]*.

Fluvoxamine in subjects who are CYP2D6 poor metabolizers

Concomitant administration of duloxetine 40 mg twice daily with fluvoxamine 100 mg, a strong CYP1A2 inhibitor, in subjects who are CYP2D6 poor metabolizers (n = 14) resulted in a 6-fold increase in duloxetine AUC and C_{max} *[see Drug Interactions (7.1)]*.

Paroxetine

Concomitant use of duloxetine (40 mg once daily) with paroxetine (20 mg once daily), a strong CYP2D6 inhibitor, increased the concentration of duloxetine AUC by about 60%, and greater degrees of inhibition are expected with higher doses of paroxetine. Duloxetine use in subjects who are CYP2D6 poor metabolizers are expected to result in similar magnitude of exposure increase (i.e. 60% AUC increase) *[see Drug Interactions (7.1)]*.

Lorazepam

Under steady-state conditions for duloxetine (60 mg Q 12 hours) and lorazepam (2 mg Q 12 hours), the pharmacokinetics of duloxetine were not affected by co-administration.

Temazepam

Under steady-state conditions for duloxetine (20 mg qhs) and temazepam (30 mg qhs), the pharmacokinetics of duloxetine were not affected by co-administration.

Drugs that Affect Gastric Acidity

Co-administration of duloxetine delayed-release capsules with aluminum- and magnesium-containing antacids (51 mEq) or duloxetine delayed-release capsules with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose *[see Drug Interactions (7.1)]*.

Clinical Studies: Effect of duloxetine on other drugs

Warfarin

Under steady-state condition for warfarin (2 to 9 mg once daily) and duloxetine (60 or 120 mg once daily), the total warfarin (protein bound plus free drug) pharmacokinetics ($AUC_{\tau,ss}$, $C_{max,ss}$ or $t_{max,ss}$) for both R- and S-warfarin (a CYP2C9 substrate) were not altered by duloxetine *[see Drug Interactions (7.1)]*.

Theophylline

In two clinical studies the average (90% confidence interval) increase in theophylline (a CYP1A2 substrate) AUC was 7% (1% to 15%) and 20% (13% to 27%) when co-administered with duloxetine (60 mg twice daily) *[see Drug Interactions (7.1)]*.

Desipramine

When duloxetine was administered (at a dose of 60 mg twice daily) in conjunction with a single 50 mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold *[see Drug Interactions (7.1)]*.

In vitro Studies

Results of in vitro studies demonstrate that duloxetine does not inhibit activity of drugs metabolized by CYP3A (e.g., oral contraceptives and other steroidal agents), and drugs metabolized by CYP2C19.

Alcohol Effect

An in vitro study showed that dose-dumping or near complete releases of duloxetine hydrochloride from Duloxetine Delayed-Release Capsules occurred within an hour in the presence of alcohol concentrations above 20%. Compared to 0% alcohol, no more than 9% of the drug was released in 2 hours in 5% alcohol. There is no in vivo study conducted for the effect of alcohol on drug exposure.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Duloxetine was administered in the diet to mice and rats for 2 years.

In female mice receiving duloxetine at 140 mg/kg/day (3 times the maximum recommended human dose (MRHD) of 120 mg/day given to children on a mg/m^2 basis), there was an increased incidence of hepatocellular adenomas and carcinomas. The no-effect dose was 50 mg/kg/day (1 time the MRHD given to children). Tumor incidence was not increased in male mice receiving duloxetine at doses up to 100 mg/kg/day (2 times the MRHD given to children).

In rats, dietary doses of duloxetine up to 27 mg/kg/day in females (1 time the MRHD given to children) and up to 36 mg/kg/day in males (1.4 time the MRHD given to children) did not increase the incidence of tumors.

Mutagenesis

Duloxetine was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) and was not clastogenic in an *in vivo* chromosomal aberration test in mouse bone marrow cells. Additionally, duloxetine was not genotoxic in an *in vitro* mammalian forward gene mutation assay in mouse lymphoma cells or in an *in vitro*

unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, and did not induce sister chromatid exchange in Chinese hamster bone marrow *in vivo*.

Impairment of Fertility

Duloxetine administered orally to either male or female rats prior to and throughout mating at doses up to 45 mg/kg/day (3 times the MRHD given to adolescents on a mg/m^2 basis) did not alter mating or fertility.

14 CLINICAL STUDIES

14.1 Major Depressive Disorder

The efficacy of Duloxetine Delayed-Release Capsules for the treatment of major depressive disorder (MDD) in adult patients is based upon adequate and well-controlled studies of another duloxetine delayed-release capsule product. The results of these adequate and well-controlled studies of duloxetine delayed-release capsules are presented below.

The efficacy of duloxetine delayed-release capsules as a treatment for MDD in adults was established in four randomized, double-blind, placebo-controlled, fixed-dose trials in adult outpatients (18 years to 83 years) meeting DSM-IV criteria for MDD:

- In Study 1 and Study 2, patients were randomized to duloxetine delayed-release capsules 60 mg once daily (N=123 and N=128, respectively) or placebo (N=122 and N=139, respectively) for 9 weeks
- In Study 3, patients were randomized to duloxetine delayed-release capsules 20 mg or 40 mg twice daily (N=86 and N=91, respectively) or placebo (N=89) for 8 weeks
- In Study 4, patients were randomized to duloxetine delayed-release capsules 40 mg or 60 mg twice daily (N=95 and N=93, respectively) or placebo (N=93) for 8 weeks.

In all four trials, duloxetine delayed-release capsules demonstrated superiority over placebo as measured by improvement in the 17-item Hamilton Depression Rating Scale (HAMD-17) total score (see Table 7). There is no evidence that doses greater than 60 mg/day confer additional benefits.

In all of these clinical trials, analyses of the relationship between treatment outcome and age, gender, and race did not suggest any differential responsiveness on the basis of these patient characteristics.

Table 7: Summary of the Primary Efficacy Results for Adult Trials in MDD

Study Number	Treatment Group	Primary Efficacy Measure: HAMD-17		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	Another Duloxetine Product (60 mg/day)[b]	21.5 (4.10)	-10.9 (0.70)	-4.9 (-6.8, -2.9)
	Placebo	21.1 (3.71)	-6.1 (0.69)	--
Study 2	Another Duloxetine Product (60 mg/day)[b]	20.3 (3.32)	-10.5 (0.71)	-2.2 (-4.0, -0.3)
	Placebo	20.5 (3.42)	-8.3 (0.67)	--
Study 3	Another Duloxetine Product (20 mg BID)[b]	18.6 (5.85)	-7.4 (0.80)	-2.4 (-4.7, -0.2)

	Another Duloxetine Product (40 mg BID)[b]	18.1 (4.52)	-8.6 (0.81)	-3.6 (-5.9, -1.4)
	Placebo	17.2 (5.11)	-5.0 (0.81)	--
Study 4	Another Duloxetine Product (40 mg BID)[b]	19.9 (3.54)	-11.0 (0.49)	-2.2 (-3.6, -0.9)
	Another Duloxetine Product (60 mg BID)[b]	20.2 (3.41)	-12.1 (0.49)	-3.3 (-4.7, -1.9)
	Placebo	19.9 (3.58)	-8.8 (0.50)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval, not adjusted for multiplicity in trials where multiple dose groups were included.

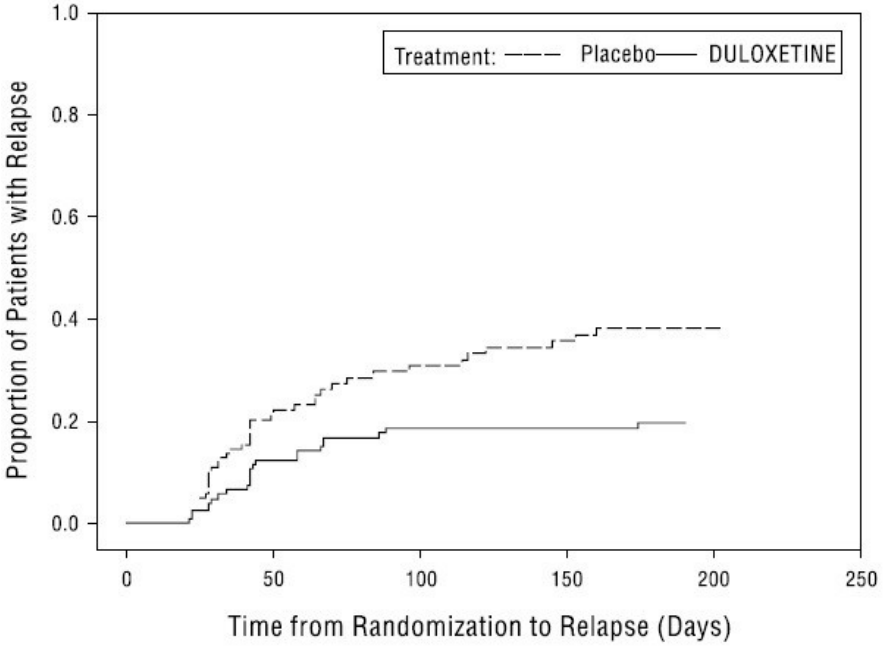
[a] Difference (drug minus placebo) in least-squares mean change from baseline.

[b] Doses statistically significantly superior to placebo.

In another trial (Study 5), 533 adult patients meeting DSM-IV criteria for MDD received duloxetine delayed-release capsules 60 mg once daily during an initial 12-week open-label treatment phase. Two hundred and seventy-eight patients who responded to open label treatment [defined as meeting the following criteria at weeks 10 and 12: a HAMD-17 total score ≤9, Clinical Global Impressions of Severity (CGI-S) ≤2, and not meeting the DSM-IV criteria for MDD] were randomly assigned to continuation of duloxetine delayed-release capsules at the same dosage (N=136) or to placebo (N=142) for 6 months.

In Study 5, patients on duloxetine delayed-release capsules experienced a statistically significantly longer time to relapse of depression than did patients on placebo (see Figure 1). Relapse was defined as an increase in the CGI-S score of ≥2 points compared with that obtained at week 12, as well as meeting the DSM-IV criteria for MDD at 2 consecutive visits at least 2 weeks apart, where the 2-week temporal criterion had to be satisfied at only the second visit.

Figure 1: Cumulative Proportion[a] of Adult Patients with MDD Relapse (Study 5)



[a] Kaplan-Meier estimator method.

14.2 Generalized Anxiety Disorder

The efficacy of Duloxetine Delayed-Release Capsules for the treatment of generalized anxiety disorder (GAD) in adults and pediatric patients 7 years of age and older is based upon adequate and well-controlled studies of another duloxetine delayed-release capsule product. The results of these adequate and well-controlled studies of duloxetine delayed-release capsules are presented below.

GAD Trials in Adults (Including Geriatric Patients)

The efficacy of duloxetine delayed-release capsules in the treatment of generalized anxiety disorder (GAD) was established in one fixed-dose randomized, double-blind, placebo-controlled trial (Study 1) and two flexible-dose randomized, double-blind, placebo-controlled trials (Studies 2 and 3) in adult outpatients between 18 years and 83 years of age meeting the DSM-IV criteria for GAD.

In Study 1 and Study 2, the starting dose was 60 mg once daily (down titration to 30 mg once daily was allowed for tolerability reasons; the dosage could be increased to 60 mg once daily). Fifteen percent of patients were down titrated. Study 3 had a starting dose of 30 mg once daily for 1 week before increasing it to 60 mg once daily.

Study 2 and Study 3 involved dose titration with duloxetine delayed-release capsules doses ranging from 60 mg once daily to 120 mg once daily (N=168 and N=162) compared to placebo (N=159 and N=161) over a 10-week treatment period. The mean dosage for completers at endpoint in these trials was 104.8 mg/day. Study 1 evaluated duloxetine delayed-release capsules dosages of 60 mg once daily (N=168) and 120 mg once daily (N=170) compared to placebo (N=175) over a 9-week treatment period. While a 120 mg/day dose was shown to be effective, there is no evidence that doses greater than 60 mg/day confer additional benefit.

In all three trials, duloxetine delayed-release capsules demonstrated superiority over placebo as measured by greater improvement in the Hamilton Anxiety Scale (HAM-A) total score (see Table 8) and by the Sheehan Disability Scale (SDS) global functional impairment score. The SDS is a composite measurement of the extent emotional symptoms disrupt patient functioning in 3 life domains: work/school, social life/leisure activities, and family life/home responsibilities.

In another trial (Study 4), 887 patients meeting DSM-IV-TR criteria for GAD received duloxetine delayed-release capsules 60 mg to 120 mg once daily during an initial 26-week open-label treatment phase. Four hundred and twenty-nine patients who responded to open-label treatment [defined as meeting the following criteria at weeks 24 and 26: a decrease from baseline HAM-A total score by at least 50% to a score no higher than 11, and a Clinical Global Impressions of Improvement (CGI-Improvement) score of 1 or 2] were randomly assigned to continuation of duloxetine delayed-release capsules at the same dosage (N=216) or to placebo (N=213) and were observed for relapse. Of the patients randomized, 73% had been in a responder status for at least 10 weeks. Relapse was defined as an increase in CGI-Severity score at least 2 points to a score ≥4 and a MINI (Mini-International Neuropsychiatric Interview) diagnosis of GAD (excluding duration), or discontinuation due to lack of efficacy. Patients taking duloxetine delayed-release capsules experienced a statistically significantly longer time to relapse of GAD than did patients taking placebo (see Figure 2).

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

GAD Trial in Geriatric Patients

The efficacy of duloxetine delayed-release capsules in the treatment of patients ≥65 years of age with GAD was established in one 10-week flexible-dose, randomized, double-blind, placebo-controlled trial in adults ≥65 years of age meeting the DSM-IV criteria for GAD (Study 5). In Study 5, the starting dose was 30 mg once daily for 2 weeks before further dose increases in 30 mg increments at treatment weeks 2, 4, and 7 up to 120 mg once daily were allowed based on investigator judgment of clinical response and tolerability. The mean dosage for patients completing the 10-week acute treatment phase was 51 mg. Patients treated with duloxetine delayed-release capsules (N=151) demonstrated significantly greater improvement compared with placebo (N=140) on mean change from baseline to endpoint as measured by the HAM-A total score (see Table 8).

GAD Trial in Pediatric Patients 7 to 17 Years of Age

The efficacy of duloxetine delayed-release capsules in the treatment of pediatric patients 7 to 17 years of age with GAD was established in one flexible-dose randomized, double-blind, placebo-controlled trial in pediatric outpatients with GAD (based on DSM-IV criteria) (Study 6).

In Study 6, the starting dose was 30 mg once daily for 2 weeks. Further dose increases in 30 mg increments up to 120 mg once daily were allowed based on investigator judgment of clinical response and tolerability. The mean dosage for patients completing the 10-week treatment phase was 57.6 mg/day. In this study, duloxetine delayed-release capsules (N=135) demonstrated superiority over placebo (N=137) from baseline to endpoint as measured by greater improvement in the Pediatric Anxiety Rating Scale (PARS) for GAD severity score (see Table 8).

Table 8: Summary of the Primary Efficacy Results for GAD Trials

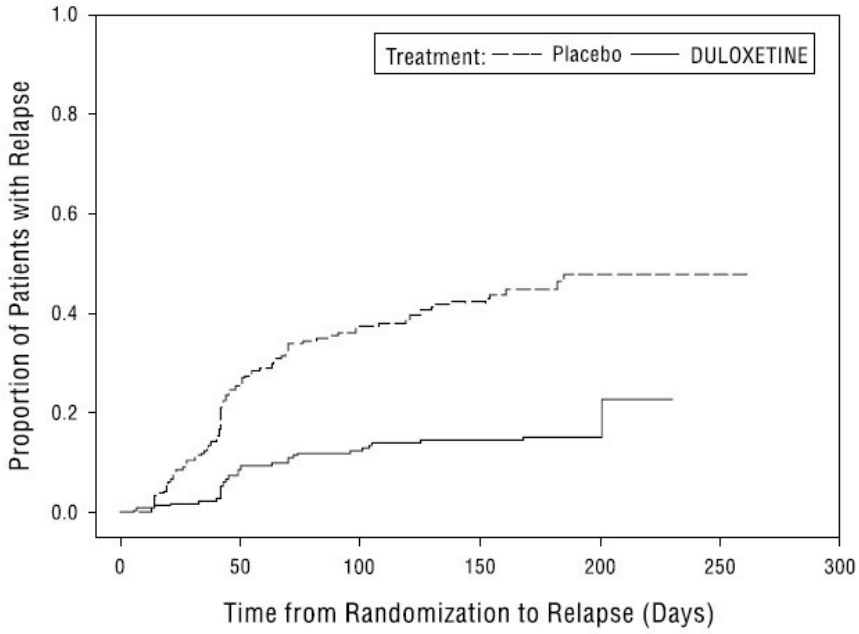
Study Number (population) (measurement)	**Treatment Group**	**Primary Efficacy Measure**		
		Mean Baseline Score (SD)	**LS Mean Change from Baseline (SE)**	**Placebo-subtracted Difference[a] (95% CI)**
Study 1 (Adult) (HAM-A)	Another Duloxetine Product (60 mg/day)[b]	25.1 (7.18)	-12.8 (0.68)	-4.4 (-6.2, -2.5)
	Another Duloxetine Product (120 mg/day)[b]	25.1 (7.24)	-12.5 (0.67)	-4.1 (-5.9, -2.3)
	Placebo	25.8 (7.66)	-8.4 (0.67)	--
Study 2 (Adult) (HAM-A)	Another Duloxetine Product (60-120 mg/day)[b]	22.5 (7.44)	-8.1 (0.70)	-2.2 (-4.2, -0.3)
	Placebo	23.5 (7.91)	-5.9 (0.70)	--
Study 3 (Adult) (HAM-A)	Another Duloxetine Product (60-120 mg/day)[b]	25.8 (5.66)	-11.8 (0.69)	-2.6 (-4.5, -0.7)
	Placebo	25.0 (5.82)	-9.2 (0.67)	--
Study 5 (Geriatric) (HAM-A)	Another Duloxetine Product (60-120 mg/day)[b]	24.6 (6.21)	-15.9 (0.63)	-4.2 (-5.9, -2.5)
	Placebo	24.5 (7.05)	-11.7 (0.67)	--
Study 6 (Pediatric) (PARS for GAD)	Another Duloxetine Product (30-120 mg/day)[b]	17.5 (1.98)	-9.7 (0.50)	-2.7 (-4.0, -1.3)
	Placebo	17.4 (2.24)	-7.1 (0.50)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval, not adjusted for multiplicity in trials where multiple dose groups were included.

[a] Difference (drug minus placebo) in least squares mean change from baseline.

[b] Dose statistically significantly superior to placebo.

Figure 2: Cumulative Proportion[a] of Adult Patients with GAD Relapse (Study 4)



[a] Kaplan-Meier estimator method.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Duloxetine Delayed-Release Capsules are available as:

80 mg: Hard shell gelatin capsules, with "ALM" printed axially on the opaque pale yellow cap and "821" printed axially on the opaque white body. Each capsule contains 89.8 mg of duloxetine hydrochloride, USP equivalent to 80 mg duloxetine.
NDC 52427-821-30, bottle of 30 capsules with a child-resistant closure

90 mg: Hard shell gelatin capsules, with "ALM" printed axially on the opaque green cap and "913" printed axially on the opaque white body. Each capsule contains 101 mg of duloxetine hydrochloride, USP equivalent to 90 mg duloxetine.
NDC 52427-913-30, bottle of 30 capsules with a child-resistant closure

120 mg: Hard shell gelatin capsules, with "ALM" printed axially on the opaque light green cap and "791" printed axially on the opaque white body. Each capsule contains 134.7 mg of duloxetine hydrochloride, USP equivalent to 120 mg duloxetine.
NDC 52427-791-30, bottle of 30 capsules with a child-resistant closure

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Suicidal Thoughts and Behaviors

Advise patients, their families, and their caregivers to look for the emergence of suicidal ideation and behavior, especially during treatment and when the dose is adjusted up or down and instruct them to report such symptoms to their healthcare provider *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Administration

Advise patients to take Duloxetine-Delayed Release Capsules on an empty stomach at least one hour before or two hours after a meal and to swallow Duloxetine Delayed-Release Capsules whole and to not chew, crush, or open the capsule (do not sprinkle contents on food or mixed with liquids) because these actions might affect the enteric coating.

Hepatotoxicity

Inform patients that severe liver problems, sometimes fatal, have been reported in patients treated with Duloxetine Delayed-Release Capsules. Instruct patients to talk to their healthcare provider immediately if they develop itching, right upper belly pain, dark urine, or yellow skin/eyes while taking Duloxetine Delayed-Release Capsules, which may be signs of liver problems. Instruct patients to talk to their healthcare provider about their alcohol consumption. Use of Duloxetine Delayed-Release Capsules with heavy alcohol intake may be associated with severe liver injury *[see Warnings and Precautions (5.2)]*.

Alcohol

Although Duloxetine Delayed-Release Capsules does not increase the impairment of mental and motor skills caused by alcohol, use of Duloxetine Delayed-Release Capsules concomitantly with heavy alcohol intake may be associated with severe liver injury *[see Warnings and Precautions (5.2), Drug Interactions (7.1)]*.

Orthostatic Hypotension, Falls and Syncope

Advise patients of the risk of orthostatic hypotension, falls and syncope, especially during the period of initial use and subsequent dose escalation, and in association with the use of concomitant drugs that might potentiate the orthostatic effect of Duloxetine Delayed-Release Capsules *[see Warnings and Precautions (5.3)]*.

Serotonin Syndrome

Caution patients about the risk of serotonin syndrome with the concomitant use of Duloxetine Delayed-Release Capsules and other serotonergic agents including triptans, tricyclic antidepressants, opioids, lithium, buspirone, tryptophan, amphetamines, and St. John's Wort *[see Contraindications (4), Warnings and Precautions (5.4), Drug Interactions (7.1)]*. Advise patients of the signs and symptoms associated with serotonin syndrome that 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 changes (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Caution patients to seek medical care immediately if they experience these symptoms.

Increased Risk of Bleeding

Caution patients about the concomitant use of Duloxetine Delayed-Release Capsules and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding. *[see Warnings and Precautions (5.5), Use in Specific Populations (8.1)]*.

Severe Skin Reactions

Caution patients that Duloxetine Delayed-Release Capsules may cause serious skin reactions. This may need to be treated in a hospital and may be life-threatening. Counsel patients to call their doctor right away or get emergency help if they have skin blisters, peeling rash, sores in their mouth, hives, or any other allergic reactions *[see Warnings and Precautions (5.6)]*.

Discontinuation of Treatment

Instruct patients that discontinuation of Duloxetine Delayed-Release Capsules may be associated with symptoms such as dizziness, headache, nausea, diarrhea, paresthesia, irritability, vomiting, insomnia, anxiety, hyperhidrosis,

and fatigue, and should be advised not to alter their dosing regimen, or stop taking Duloxetine Delayed-Release Capsules without consulting their healthcare provider *[see Warnings and Precautions (5.7)]*.

Activation of Mania or Hypomania

Adequately screen patients with depressive symptoms for risk of bipolar disorder (e.g. family history of suicide, bipolar disorder, and depression) prior to initiating treatment with Duloxetine Delayed-Release Capsules. Advise patients to report any signs or symptoms of a manic reaction such as greatly increased energy, severe trouble sleeping, racing thoughts, reckless behavior, talking more or faster than usual, unusually grand ideas, and excessive happiness or irritability *[see Warnings and Precautions (5.8)]*.

Angle-Closure Glaucoma

Advise patients that taking Duloxetine Delayed-Release Capsules can cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle-closure glaucoma. Pre-existing glaucoma is almost always open-angle glaucoma because angle-closure glaucoma, when diagnosed, can be treated definitively with iridectomy. Open-angle glaucoma is not a risk factor for angle-closure glaucoma. Patients may wish to be examined to determine whether they are susceptible to angle-closure, and have a prophylactic procedure (e.g., iridectomy), if they are susceptible *[see Warnings and Precautions (5.9)]*.

Seizures

Advise patients to inform their healthcare provider if they have a history of seizure disorder *[see Warnings and Precautions (5.10)]*.

Effects on Blood Pressure

Caution patients that Duloxetine Delayed-Release Capsules may cause an increase in blood pressure *[see Warnings and Precautions (5.11)]*.

Concomitant Medications

Advise patients to inform their healthcare provider if they are taking, or plan to take, any prescription or over-the-counter medications, since there is a potential for interactions *[see Dosage and Administration (2.7), Contraindications (4), Warnings and Precautions (5.4), Drug Interactions (7.1)]*.

Hyponatremia

Advise patients that hyponatremia has been reported as a result of treatment with SNRIs and SSRIs, including Duloxetine Delayed-Release Capsules. Advise patients of the signs and symptoms of hyponatremia *[see Warnings and Precautions (5.12)]*.

Concomitant Illnesses

Advise patients to inform their healthcare provider about all of their medical conditions *[see Warnings and Precautions (5.13)]*.

Urinary Hesitation and Retention

Duloxetine Delayed-Release Capsules is in a class of medicines that may affect urination. Instruct patients to consult with their healthcare provider if they develop any problems with urine flow *[see Warnings and Precautions (5.14)]*.

Sexual Dysfunction

Advise patients that use of Duloxetine Delayed-Release Capsules may cause symptoms of sexual dysfunction in both male and female patients. Inform patients that they should discuss any changes in sexual function and potential management strategies with their healthcare provider *[see Warnings and Precautions (5.15)]*.

Pregnancy

- Advise women to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with Duloxetine Delayed-Release Capsules.

- Advise pregnant women or patients who intend to become pregnant that Duloxetine Delayed-Release Capsules may increase the risk of neonatal complications requiring prolonged hospitalization, respiratory support, and tube feeding.
- Advise pregnant women that there is a risk of relapse with discontinuation of antidepressants.
- Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Duloxetine Delayed-Release Capsules during pregnancy *[see Use in Specific Populations (8.1)]*.
- Advise pregnant women or patients who intend to become pregnant that the use of Duloxetine Delayed-Release Capsules in the month before delivery may be associated with an increased risk of postpartum hemorrhage *[see Use in Specific Populations (8.1) and Warnings and Precautions (5.5)]*.

Lactation

Advise breastfeeding women using Duloxetine Delayed-Release Capsules to monitor infants for sedation, poor feeding and poor weight gain and to seek medical care if they notice these signs *[see Use in Specific Populations (8.2)]*.

Interference with Psychomotor Performance

Duloxetine Delayed-Release Capsules may be associated with sedation and dizziness. Therefore, 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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Information about Duloxetine Delayed-Release Capsules intended for US healthcare professionals is available at www.duloxetinecaps.com.