DULOXETINE HYDROCHLORIDE- duloxetine hydrochloride capsule, delayed release pellets
DIRECT RX

DULOXETINE HYDROCHLORIDE

BOXED WARNING SECTION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older [see Warnings and Precautions (5.1)].

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber [see Warnings and Precautions (5.1)].

Duloxetine Delayed-release Capsules are not approved for use in pediatric patients [see Use in Specific Populations (8.4)].

INDICATIONS & USAGE SECTION

1.1 Major Depressive Disorder

Duloxetine Delayed-release Capsules are indicated for the treatment of major depressive disorder (MDD). The efficacy of Duloxetine Delayed-release Capsules was established in four short-term and one maintenance trial in adults [see Clinical Studies (14.1)].

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or a suicide attempt or suicidal ideation.

1.2 Generalized Anxiety Disorder

Duloxetine Delayed-release Capsules are indicated for the treatment of generalized anxiety disorder (GAD). The efficacy of Duloxetine Delayed-release Capsules was established in three short-term trials and one maintenance trial in adults [see Clinical Studies (14.2)].

Generalized anxiety disorder is defined by the DSM-IV as excessive anxiety and worry, present more days than not, for at least 6 months. The excessive anxiety and worry must be difficult to control and must cause significant distress or impairment in normal functioning. It must be associated with at least 3 of the following 6 symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and/or sleep disturbance.

1.3 Diabetic Peripheral Neuropathic Pain

Duloxetine Delayed-release Capsules are indicated for the management of neuropathic pain (DPNP) associated with diabetic peripheral neuropathy [see Clinical Studies (14.3)].

1.5 Chronic Musculoskeletal Pain

Duloxetine Delayed-release Capsules are indicated for the management of chronic musculoskeletal pain. This has been established in studies in patients with chronic low back pain (CLBP) and chronic

pain due to osteoarthritis [see Clinical Studies (14.5)].

DOSAGE & ADMINISTRATION SECTION

Duloxetine Delayed-release Capsules should be swallowed whole and should not be chewed or crushed, nor should the capsule be opened and its contents sprinkled on food or mixed with liquids. All of these might affect the enteric coating. Duloxetine Delayed-release Capsules can be given without regard to meals.

2.1 Initial Treatment

Major Depressive Disorder — Duloxetine Delayed-release Capsules should be administered at a total dose of 40 mg/day (given as 20 mg twice daily) to 60 mg/day (given either once daily or as 30 mg twice daily). For some patients, it may be desirable to start at 30 mg once daily for 1 week, to allow patients to adjust to the medication before increasing to 60 mg once daily. While a 120 mg/day dose was shown to be effective, there is no evidence that doses greater than 60 mg/day confer any additional benefits. The safety of doses above 120 mg/day has not been adequately evaluated [see Clinical Studies (14.1)].

Generalized Anxiety Disorder — For most patients, the recommended starting dose for Duloxetine Delayed-release Capsules is 60 mg administered once daily. For some patients, it may be desirable to start at 30 mg once daily for 1 week, to allow patients to adjust to the medication before increasing to 60 mg once daily. While a 120 mg once daily dose was shown to be effective, there is no evidence that doses greater than 60 mg/day confer additional benefit. Nevertheless, if a decision is made to increase the dose beyond 60 mg once daily, dose increases should be in increments of 30 mg once daily. The safety of doses above 120 mg once daily has not been adequately evaluated [see Clinical Studies (14.2)].

Diabetic Peripheral Neuropathic Pain — The recommended dose for Duloxetine Delayed-release Capsules is 60 mg administered once daily. There is no evidence that doses higher than 60 mg confer additional significant benefit and the higher dose is clearly less well tolerated [see Clinical Studies (14.3)]. For patients for whom tolerability is a concern, a lower starting dose may be considered.

Since diabetes is frequently complicated by renal disease, a lower starting dose and gradual increase in dose should be considered for patients with renal impairment [see Dosage and Administration (2.3), Use in Specific Populations (8.10), and Clinical Pharmacology (12.3)].

Chronic Musculoskeletal Pain — The recommended dose for Duloxetine Delayed-release Capsules is 60 mg once daily. Dosing may be started at 30 mg for one week, to allow patients to adjust to the medication before increasing to 60 mg once daily. There is no evidence that higher doses confer additional benefit, even in patients who do not respond to a 60 mg dose, and higher doses are associated with a higher rate of adverse reactions [see Clinical Studies (14.5)].

2.2 Maintenance/Continuation/Extended Treatment

Major Depressive Disorder — It is generally agreed that acute episodes of major depression require several months or longer of sustained pharmacologic therapy. Maintenance of efficacy in MDD was demonstrated with Duloxetine Delayed-release Capsules as monotherapy. Duloxetine Delayed-release Capsules should be administered at a total dose of 60 mg once daily. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment [see Clinical Studies (14.1)].

Generalized Anxiety Disorder — It is generally agreed that episodes of generalized anxiety disorder require several months or longer of sustained pharmacological therapy. Maintenance of efficacy in GAD was demonstrated with Duloxetine Delayed-release Capsules as monotherapy. Duloxetine Delayed-release Capsules should be administered in a dose range of 60-120 mg once daily. Patients should be periodically reassessed to determine the continued need for maintenance treatment and the appropriate dose for such treatment [see Clinical Studies (14.2)].

Diabetic Peripheral Neuropathic Pain — As the progression of diabetic peripheral neuropathy is highly variable and management of pain is empirical, the effectiveness of Duloxetine Delayed-release Capsules must be assessed individually. Efficacy beyond 12 weeks has not been systematically studied in placebo-controlled trials.

Chronic Musculoskeletal Pain — The efficacy of Duloxetine Delayed-release Capsules has not been established in placebo-controlled studies beyond 13 weeks.

2.3 Dosing in Special Populations

Hepatic Insufficiency — It is recommended that Duloxetine Delayed-release Capsules should ordinarily not be administered to patients with any hepatic insufficiency [see Warnings and Precautions (5.13) and Use in Specific Populations (8.9)].

Severe Renal Impairment — Duloxetine Delayed-release Capsules are not recommended for patients with end-stage renal disease or severe renal impairment (estimated creatinine clearance <30 mL/min) [see Warnings and Precautions (5.13) and Use in Specific Populations (8.10)].

Elderly Patients — No dose adjustment is recommended for elderly patients on the basis of age. As with any drug, caution should be exercised in treating the elderly. When individualizing the dosage in elderly patients, extra care should be taken when increasing the dose [see Use in Specific Populations (8.5)].

Pregnant Women — There are no adequate and well-controlled studies in pregnant women; therefore, Duloxetine Delayed-release Capsules should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus [see Use in Specific Populations (8.1)].

Nursing Mothers — Because the safety of duloxetine in infants is not known, nursing while on Duloxetine Delayed-release Capsules is not recommended [see Use in Specific Populations (8.3)].

2.4 Discontinuing Duloxetine Delayed-release Capsules

Symptoms associated with discontinuation of Duloxetine Delayed-release Capsules and other SSRIs and SNRIs have been reported. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible [see Warnings and Precautions (5.7)].

2.5 Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders

At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with Duloxetine Delayed-release Capsules. Conversely, at least 5 days should be allowed after stopping Duloxetine Delayed-release Capsules before starting an MAOI intended to treat psychiatric disorders [see Contraindications (4.1)].

2.6 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 (4.1)]

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)].

CONTRAINDICATIONS SECTION

4.1 Monoamine Oxidase Inhibitors (MAOIs)

The use of MAOIs intended to treat psychiatric disorders with Duloxetine Delayed-release Capsules or within 5 days of stopping treatment with Duloxetine Delayed-release Capsules is contraindicated because of an increased risk of serotonin syndrome. The use of Duloxetine Delayed-release Capsules within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated [see Dosage and Administration (2.5) and Warnings and Precautions (5.4)].

Starting Duloxetine Delayed-release Capsules in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome [see Dosage and Administration (2.6) and Warnings and Precautions (5.4)].

4.2 Uncontrolled Narrow-Angle Glaucoma

In clinical trials, Duloxetine Delayed-release Capsule use was associated with an increased risk of mydriasis; therefore, its use should be avoided in patients with uncontrolled narrow-angle glaucoma [see Warnings and Precautions (5.13)].

WARNINGS AND PRECAUTIONS SECTION

5.1 Suicidal Thoughts and Behaviors in Adolescents and Young Adults

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

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

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk of differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

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

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

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

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

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that discontinuation can be associated with certain symptoms [see Dosage and Administration (2.4) and Warnings and Precautions (5.7) for descriptions of the risks of discontinuation of Duloxetine Delayed-release Capsules].

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Duloxetine Delayed-release Capsules should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

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

5.2 Hepatotoxicity

There have been reports of hepatic failure, sometimes fatal, in patients treated with Duloxetine Delayed-release Capsules. These cases have presented as hepatitis with abdominal pain, hepatomegaly, and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Duloxetine Delayed-release Capsules should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established.

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

Duloxetine Delayed-release Capsules increased the risk of elevation of serum transaminase levels in development program clinical trials. Liver transaminase elevations resulted in the discontinuation of 0.3% (89/29,435) of Duloxetine Delayed-release Capsules-treated patients. In most patients, the median time to detection of the transaminase elevation was about two months. In placebo-controlled trials in any indication, for patients with normal and abnormal baseline ALT values, elevation of ALT >3 times the upper limit of normal occurred in 1.37% (132/9611) of Duloxetine Delayed-release Capsules-treated patients compared to 0.49% (35/7182) of placebo-treated patients. In placebo-controlled studies using a fixed dose design, there was evidence of a dose response relationship for ALT and AST elevation of >3 times the upper limit of normal and >5 times the upper limit of normal, respectively.

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

5.3 Orthostatic Hypotension and Syncope

Orthostatic hypotension and syncope have been reported with therapeutic doses of duloxetine. Syncope and orthostatic hypotension tend to occur within the first week of therapy but can occur at any time during duloxetine treatment, particularly after dose increases. The risk of blood pressure decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as antihypertensives) or are potent CYP1A2 inhibitors [see Warnings and Precautions (5.11) and Drug Interactions (7.1)] and in patients taking duloxetine at doses above 60 mg daily. Consideration should be given to discontinuing duloxetine in patients who experience symptomatic orthostatic hypotension and/or syncope during duloxetine therapy.

5.4 Serotonin Syndrome

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

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

The concomitant use of Duloxetine Delayed-release Capsules with MAOIs intended to treat psychiatric disorders is contraindicated. Duloxetine Delayed-release Capsules should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of

methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking Duloxetine Delayed-release Capsules. Duloxetine Delayed-release Capsules should be discontinued before initiating treatment with the MAOI [see Dosage and Administration (2.5, 2.6), and Contraindications (4.1)].

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

5.5 Abnormal Bleeding

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

Patients should be cautioned about the risk of bleeding associated with the concomitant use of duloxetine and NSAIDs, aspirin, or other drugs that affect coagulation.

5.6 Severe Skin Reactions

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

Duloxetine Delayed-release Capsules should be discontinued at the first appearance of blisters, peeling rash, mucosal erosions, or any other sign of hypersensitivity if no other etiology can be identified.

5.7 Discontinuation of Treatment with Duloxetine Delayed-release Capsules

Discontinuation symptoms have been systematically evaluated in patients taking duloxetine. Following abrupt or tapered discontinuation in placebo-controlled clinical trials, the following symptoms occurred at 1% or greater and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness, headache, nausea, diarrhea, paresthesia, irritability, vomiting, insomnia, anxiety, hyperhidrosis, and fatigue.

During marketing of other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe.

Patients should be monitored for these symptoms when discontinuing treatment with Duloxetine Delayed-release Capsules. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate [see Dosage and Administration (2.4)].

5.8 Activation of Mania/Hypomania

In placebo-controlled trials in patients with major depressive disorder, activation of mania or hypomania was reported in 0.1% (2/2489) of duloxetine-treated patients and 0.1% (1/1625) of placebo-treated patients. No activation of mania or hypomania was reported in GAD placebo-controlled trials. Activation of mania or hypomania has been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs effective in the treatment of major depressive disorder. As with these other agents, Duloxetine Delayed-release Capsules should be used cautiously in patients with a history of mania.

5.9 Seizures

Duloxetine has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. In placebo-controlled clinical trials, seizures/convulsions occurred in 0.03% (3/10,524) of patients treated with duloxetine and 0.01% (1/7699) of patients treated with placebo. Duloxetine Delayed-release Capsules should be prescribed with care in patients with a history of a seizure disorder.

5.10 Effect on Blood Pressure

In placebo-controlled clinical trials across indications from baseline to endpoint, duloxetine treatment was associated with mean increases of 0.5 mm Hg in systolic blood pressure and 0.8 mm Hg in diastolic blood pressure compared to mean decreases of 0.6 mm Hg systolic and 0.4 mm Hg diastolic in placebo-treated patients. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. In a clinical pharmacology study designed to evaluate the effects of duloxetine on various parameters, including blood pressure at supratherapeutic doses with an accelerated dose titration, there was evidence of increases in supine blood pressure at doses up to 200 mg twice daily. At the highest 200 mg twice daily dose, the increase in mean pulse rate was 5.0 to 6.8 beats and increases in mean blood pressure were 4.7 to 6.8 mm Hg (systolic) and 4.5 to 7 mm Hg (diastolic) up to 12 hours after dosing.

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

5.11 Clinically Important Drug Interactions

Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Potential for Other Drugs to Affect Duloxetine Delayed-release Capsules

CYP1A2 Inhibitors — Co-administration of Duloxetine Delayed-release Capsules with potent CYP1A2 inhibitors should be avoided [see Drug Interactions (7.1)].

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

Potential for Duloxetine Delayed-release Capsules to Affect Other Drugs

Drugs Metabolized by CYP2D6 — Co-administration of Duloxetine Delayed-release Capsules with drugs that are extensively metabolized by CYP2D6 and that have a narrow therapeutic index, including certain antidepressants (tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), phenothiazines and Type 1C antiarrhythmics (e.g., propafenone, flecainide), should be approached with caution. Plasma TCA concentrations may need to be monitored and the dose of the TCA may need to be reduced if a TCA is co-administered with Duloxetine Delayed-release Capsules. Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, Duloxetine Delayed-release Capsules and thioridazine should not be co-administered [see Drug Interactions (7.9)].

Other Clinically Important Drug Interactions

Alcohol — Use of Duloxetine Delayed-release Capsules concomitantly with heavy alcohol intake may be associated with severe liver injury. For this reason, Duloxetine Delayed-release Capsules should

not be prescribed for patients with substantial alcohol use [see Warnings and Precautions (5.2) and Drug Interactions (7.15)].

CNS Acting Drugs — Given the primary CNS effects of Duloxetine Delayed-release Capsules, it should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action [see Warnings and Precautions (5.11) and Drug Interactions (7.16)].

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 and appeared to be reversible when Duloxetine Delayed-release Capsules were discontinued. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk [see Use in Specific Populations (8.5)]. Discontinuation of Duloxetine Delayed-release Capsules should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. More severe and/or acute cases have been associated with hallucination, syncope, seizure, coma, respiratory arrest, and death.

5.13 Use in Patients with Concomitant Illness

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

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

Hepatic Insufficiency — Duloxetine Delayed-release Capsules should ordinarily not be used in patients with hepatic insufficiency [see Dosage and Administration (2.3), Warnings and Precautions (5.2), and Use in Specific Populations (8.9)].

Severe Renal Impairment — Duloxetine Delayed-release Capsules should ordinarily not be used in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min). Increased plasma concentration of duloxetine, and especially of its metabolites, occur in patients with end-stage renal disease (requiring dialysis) [see Dosage and Administration (2.3) and Use in Specific Populations (8.10)].

Controlled Narrow-Angle Glaucoma — In clinical trials, Duloxetine Delayed-release Capsules were associated with an increased risk of mydriasis; therefore, it should be used cautiously in patients with controlled narrow-angle glaucoma [see Contraindications (4.2)].

Glycemic Control in Patients with Diabetes — As observed in DPNP trials, Duloxetine Delayed-release Capsules treatment worsens glycemic control in some patients with diabetes. In three clinical trials of Duloxetine Delayed-release Capsules for the management of neuropathic pain associated with diabetic peripheral neuropathy, the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 176 mg/dL, and the mean baseline hemoglobin A1c (HbA1c) was 7.8%. In the 12-week acute treatment phase of these studies, Duloxetine Delayed-release Capsules was associated with a small increase in mean fasting blood glucose as compared to placebo. In the extension phase of these studies, which lasted up to 52 weeks, mean fasting blood glucose increased by 12 mg/dL

in the Duloxetine Delayed-release Capsules group and decreased by 11.5 mg/dL in the routine care group. HbA1c increased by 0.5% in the Duloxetine Delayed-release Capsules and by 0.2% in the routine care groups.

5.14 Urinary Hesitation and Retention

Duloxetine Delayed-release Capsules are in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during treatment with Duloxetine Delayed-release Capsules, consideration should be given to the possibility that they might be drug-related.

In post marketing experience, cases of urinary retention have been observed. In some instances of urinary retention associated with duloxetine use, hospitalization and/or catheterization has been needed.

5.15 Laboratory Tests

No specific laboratory tests are recommended.

ADVERSE REACTIONS SECTION

6.1 Clinical Trial Data Sources

The data described below reflect exposure to duloxetine in placebo-controlled trials for MDD (N=2489), GAD (N=910), OA (N=239), CLBP (N=600), and DPNP (N=906). The population studied was 17 to 91 years of age; 65.5%, 62.5%, 61.5%, and 42.9% female; and 86.5%, 81.2%, 86.2%, and 74.0% Caucasian for MDD, GAD, OA and CLBP, DPNP, respectively. Most patients received doses of a total of 60 to 120 mg per day [see Clinical Studies (14)].

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

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.

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

Major Depressive Disorder — Approximately 9% (209/2327) of the patients who received duloxetine in placebo-controlled trials for MDD discontinued treatment due to an adverse reaction, compared with 4.7% (68/1460) of the patients receiving placebo. Nausea (duloxetine 1.3%, placebo 0.5%) was the only common adverse reaction reported as a reason for discontinuation and considered to be drug-related (i.e., discontinuation occurring in at least 1% of the duloxetine-treated patients and at a rate of at least twice that of placebo).

Generalized Anxiety Disorder — Approximately 15.3% (102/668) of the patients who received duloxetine in placebo-controlled trials for GAD discontinued treatment due to an adverse reaction, compared with 4.0% (20/495) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 3.7%, placebo 0.2%), and vomiting (duloxetine 1.3%, placebo 0.0%), and dizziness (duloxetine 1.0%, placebo 0.2%).

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

0.0%).

Chronic Pain due to Osteoarthritis — Approximately 16.3% (39/239) of the patients who received duloxetine in 13-week, placebo-controlled trials for chronic pain due to OA discontinued treatment due to an adverse reaction, compared with 5.6% (14/248) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 2.9%, placebo 0.8%) and asthenia (duloxetine 1.3%, placebo 0.0%).

Chronic Low Back Pain — Approximately 16.5% (99/600) of the patients who received duloxetine in 13-week, placebo-controlled trials for CLBP discontinued treatment due to an adverse reaction, compared with 6.3% (28/441) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 3.0%, placebo 0.7%), and somnolence (duloxetine 1.0%, placebo 0.0%).

6.3 Most Common Adverse Reactions

Pooled Trials for all Approved Indications — The most commonly observed adverse reactions in Duloxetine Delayed-release Capsules-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.

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

Chronic Pain due to Osteoarthritis — The most commonly observed adverse reactions in Duloxetine Delayed-release Capsules -treated patients (as defined above) were nausea, fatigue, and constipation.

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

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

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

Table 2: Treatment-Emergent Adverse Reactions: Incidence of 5% or More in Placebo-Controlled Trials of Approved Indications *

Adverse Reaction	**Percentage of Patients Reporting Reaction**	
	Duloxetine Delayed-release Capsules (N=6020)	**Placebo (N=3962)**
Nausea	24	8
Headache	14	13
Dry mouth	13	5
Fatigue †	10	5
Somnolence ‡, §	10	3
Insomnia ‡, ¶	10	6
Dizziness	10	5
Constipation ‡	10	4
Diarrhea	9	6
Decreased appetite ‡, #	8	2

Hyperhidrosis	7	2

*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.
†Also includes asthenia.
‡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.
§Also includes hypersomnia and sedation. ¶Also includes middle insomnia, early morning awakening, and initial insomnia. #Also includes anorexia.

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

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

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

System Organ Class / Adverse Reaction	**Percentage of Patients Reporting Reaction**	
	Duloxetine Delayed-release Capsules (N=2995)	**Placebo (N=1955)**
Cardiac Disorders		
Palpitations	2	2
Eye Disorders		
Vision blurred	3	2
Gastrointestinal Disorders		
Nausea	25	9
Dry mouth	15	6
Diarrhea	10	7
Constipation †	10	4
Abdominal pain ‡	4	4
Vomiting	5	2
General Disorders and		

Administration Site Conditions		
Fatigue §	10	6
Investigations		
Weight decreased †	2	<1
Metabolism and Nutrition Disorders		
Decreased appetite ¶	7	2
Nervous System Disorders		
Dizziness	10	6
Somnolence #	10	4
Tremor	3	<1
Psychiatric Disorders		
Insomnia Þ	10	6
Agitation ß	5	3
Anxiety	3	2
Libido decreased à	4	1
Orgasm abnormal †, è	3	<1
Abnormal dreams ð	2	1
Reproductive System and Breast Disorders		
Erectile dysfunction ø	4	1
Ejaculation delayed †, ø	3	<1
Ejaculation disorder ø, ý	2	<1
Respiratory, Thoracic, and Mediastinal Disorders		
Yawning	2	<1
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	6	2
Vascular Disorders		
Hot flush	2	<1

*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. †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. ‡Also includes abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort, and gastrointestinal pain §Also includes asthenia ¶Also includes anorexia #Also includes hypersomnia and sedation ÞAlso includes middle insomnia, early morning awakening and initial insomnia ßAlso includes

feeling jittery, nervousness, restlessness, tension and psychomotor agitation àAlso includes loss of libido èAlso includes anorgasmia ðAlso includes nightmare øMale patients only ýAlso includes ejaculation failure and ejaculation dysfunction

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

Table 4: Treatment-Emergent Adverse Reactions: Incidence of 2% or More in DPNP, FM, OA, and CLBP Placebo-Controlled Trials *

System Organ Class / Adverse Reaction	Percentage of Patients Reporting Reaction	
	Duloxetine Delayed-release Capsules (N=2621)	Placebo (N=1672)
Gastrointestinal Disorders		
Nausea	23	7
Dry Mouth †	11	3
Constipation †	10	3
Diarrhea	9	6
Abdominal Pain ‡	6	5
Vomiting	3	2
Dyspepsia §	2	1
General Disorders and Administration Site Conditions		
Fatigue ¶	11	5
Infections and Infestations		
Nasopharyngitis	5	4
Upper Respiratory Tract Infection	4	4
Influenza	3	2
Metabolism and Nutrition Disorders		
Decreased Appetite †, #	9	1
Musculoskeletal and Connective Tissue		
Musculoskeletal Pain †, Þ	4	4
Muscle Spasms	3	2
Nervous System Disorders		
Headache	13	9
Somnolence †, ß	12	3
Dizziness	10	5
Paraesthesia à	2	2
Tremor †	2	<1
Psychiatric Disorders		
Insomnia †, è	10	6

Agitation ð	3	<1
Reproductive System and Breast Disorders		
Erectile Dysfunction †, ø	4	<1
Ejaculation Disorder ý	2	<1
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	3	2
Oropharyngeal Pain †	2	2
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	6	1
Vascular Disorders		
Flushing £	3	1

*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. †Incidence of 120 mg/day is significantly greater than the incidence for 60 mg/day. ‡Also includes abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness and gastrointestinal pain §Also includes stomach discomfort ¶Also includes asthenia #Also includes anorexia ÞAlso includes myalgia and neck pain ßAlso includes hypersomnia and sedation àAlso includes hypoaesthesia, hypoaesthesia facial and paraesthesia oral èAlso includes middle insomnia, early morning awakening and initial insomnia ðAlso includes feeling jittery, nervousness, restlessness, tension and psychomotor hyperactivity øMale patients only (N=885 for duloxetine, 494 for placebo) ýMale patients only (N=885 for duloxetine, 494 for placebo). Also includes ejaculation failure £Also includes hot flush

6.6 Effects on Male and Female Sexual Function

Changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of psychiatric disorders or diabetes, but they may also be a consequence of pharmacologic treatment. Because adverse sexual reactions are presumed to be voluntarily underreported, the Arizona Sexual Experience Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in 4 MDD placebo-controlled trials. In these trials, as shown in Table 5 below, patients treated with Duloxetine Delayed-release Capsules experienced significantly more sexual dysfunction,

as measured by the total score on the ASEX, than did patients treated with placebo. Gender analysis showed that this difference occurred only in males. Males treated with Duloxetine Delayed-release Capsules experienced more difficulty with ability to reach orgasm (ASEX Item 4) than males treated with placebo. Females did not experience more sexual dysfunction on Duloxetine Delayed-release Capsules than on placebo as measured by ASEX total score. Negative numbers signify an improvement from a baseline level of dysfunction, which is commonly seen in depressed patients. Physicians should routinely inquire about possible sexual side effects.

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

	Male Patients *		**Female Patients ***	
Duloxetine Delayed-release Capsules (n=175)	**Placebo (n=83)**	**Duloxetine Delayed-release Capsules (n=241)**	**Placebo (n=126)**	
ASEX Total (Items 1-5)	0.56 †	-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 ‡	-0.24	-0.09	-0.13
Item 5 — Orgasm satisfaction	0.09	-0.13	-0.11	-0.17

*n=Number of patients with non-missing change score for ASEX total †p=0.013 versus placebo ‡p<0.001 versus placebo

6.7 Vital Sign Changes

In placebo-controlled clinical trials across approved indications for change from baseline to endpoint, duloxetine treatment was associated with mean increases of 0.07 mm Hg in systolic blood pressure and 0.62 mm Hg in diastolic blood pressure compared to mean decreases of 1.31 mm Hg systolic and 0.73 mm Hg diastolic in placebo-treated patients. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure [see Warnings and Precautions (5.3 and 5.10)].

Duloxetine treatment, for up to 26 weeks in placebo-controlled trials across approved indications, typically caused a small increase in heart rate for change from baseline to endpoint compared to placebo of up to 1.40 beats per minute.

6.8 Weight Changes

In placebo-controlled clinical trials, MDD and GAD patients treated with Duloxetine Delayed-release Capsules for up to 10 weeks experienced a mean weight loss of approximately 0.5 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. In studies of DPNP, patients treated with Duloxetine Delayed-release Capsules for up to 26 weeks experienced a mean weight loss of approximately 0.6 kg compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. In one long-term CLBP 54-week study (13-week, placebo-controlled acute phase and 41-week,

uncontrolled extension phase), duloxetine patients had a mean weight decrease of 0.6 kg in 13 weeks of acute phase compared to study entry, then a mean weight increase of 1.4 kg in 41 weeks of extension phase compared to end of acute phase.

6.9 Laboratory Changes

Duloxetine Delayed-release Capsule treatment in placebo-controlled clinical trials across approved indications, was associated with small mean increases from baseline to endpoint in ALT, AST, CPK, and alkaline phosphatase; infrequent, modest, transient, abnormal values were observed for these analytes in Duloxetine Delayed-release Capsules-treated patients when compared with placebo-treated patients [see Warnings and Precautions (5.2)].

6.10 Electrocardiogram Changes

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

6.11 Other Adverse Reactions Observed During the Premarketing and Postmarketing Clinical Trial Evaluation of Duloxetine

Following is a list of treatment-emergent adverse reactions reported by patients treated with duloxetine in clinical trials. In clinical trials of all indications, 29,435 patients were treated with duloxetine. Of these, 30.4% (8953) took duloxetine for at least 6 months, and 14.7% (4317) 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 and tachycardia.

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

Endocrine Disorders — Infrequent: hypothyroidism.

Eye Disorders — Frequent: vision blurred; Infrequent: diplopia, and visual disturbance.

Gastrointestinal Disorders — Frequent: flatulence; Infrequent: eructation, gastritis, halitosis, and stomatitis; Rare: gastric ulcer, hematochezia, and melena.

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

Infections and Infestations — Infrequent: gastroenteritis and laryngitis.

Investigations — Frequent: weight increased; 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 parasthesia/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 — Infrequent: dysuria, micturition urgency, nocturia, polyuria, and urine

odor abnormal.

Reproductive System and Breast Disorders — Frequent: anorgasmia/orgasm abnormal; Infrequent: menopausal symptoms, and sexual dysfunction.

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

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

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

6.12 Postmarketing Spontaneous Reports

The following adverse reactions have been identified during postapproval 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: anaphylactic reaction, aggression and anger (particularly early in treatment or after treatment discontinuation), angioneurotic edema, extrapyramidal disorder, galactorrhea, glaucoma, 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.

DRUG INTERACTIONS SECTION

Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

7.1 Inhibitors of CYP1A2

When duloxetine 60 mg was co-administered with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to male subjects (n=14) duloxetine AUC was increased approximately 6-fold, the Cmax was increased about 2.5-fold, and duloxetine t1/2 was increased approximately 3-fold. Other drugs that inhibit CYP1A2 metabolism include cimetidine and quinolone antimicrobials such as ciprofloxacin and enoxacin [see Warnings and Precautions (5.11)].

7.2 Inhibitors of CYP2D6

Concomitant use of duloxetine (40 mg once daily) with paroxetine (20 mg once daily) increased the concentration of duloxetine AUC by about 60%, and greater degrees of inhibition are expected with higher doses of paroxetine. Similar effects would be expected with other potent CYP2D6 inhibitors (e.g., fluoxetine, quinidine) [see Warnings and Precautions (5.11)].

7.3 Dual Inhibition of CYP1A2 and CYP2D6

Concomitant administration of duloxetine 40 mg twice daily with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to CYP2D6 poor metabolizer subjects (n=14) resulted in a 6-fold increase in duloxetine AUC and Cmax.

7.4 Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are co-administered with warfarin. Concomitant administration of warfarin (2-9 mg once daily) under steady

state conditions with duloxetine 60 or 120 mg once daily for up to 14 days in healthy subjects (n=15) did not significantly change INR from baseline (mean INR changes ranged from 0.05 to +0.07). The total warfarin (protein bound plus free drug) pharmacokinetics (AUCT,SS, Cmax,ss or tmax,ss) for both R- and S-warfarin were not altered by duloxetine. Because of the potential effect of duloxetine on platelets, patients receiving warfarin therapy should be carefully monitored when duloxetine is initiated or discontinued [see Warnings and Precautions (5.5)].

7.5 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.

7.6 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.

7.7 Drugs that Affect Gastric Acidity

Duloxetine Delayed-release Capsules have an enteric coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. In extremely acidic conditions, Duloxetine Delayed-release Capsules, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using Duloxetine Delayed-release Capsules in patients with conditions that may slow gastric emptying (e.g., some diabetics). Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. However, 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. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption [see Warnings and Precautions (5.13)].

7.8 Drugs Metabolized by CYP1A2

In vitro drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity. Therefore, an increase in the metabolism of CYP1A2 substrates (e.g., theophylline, caffeine) resulting from induction is not anticipated, although clinical studies of induction have not been performed. Duloxetine is an inhibitor of the CYP1A2 isoform in in vitro studies, and in two clinical studies the average (90% confidence interval) increase in theophylline AUC was 7% (1%-15%) and 20% (13%-27%) when co-administered with duloxetine (60 mg twice daily).

7.9 Drugs Metabolized by CYP2D6

Duloxetine is a moderate inhibitor of CYP2D6. 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 Warnings and Precautions (5.11)].

7.10 Drugs Metabolized by CYP2C9

Results of in vitro studies demonstrate that duloxetine does not inhibit activity. In a clinical study, the pharmacokinetics of S-warfarin, a CYP2C9 substrate, were not significantly affected by duloxetine [see Drug Interactions (7.4)].

7.11 Drugs Metabolized by CYP3A

Results of in vitro studies demonstrate that duloxetine does not inhibit or induce CYP3A activity. Therefore, an increase or decrease in the metabolism of CYP3A substrates (e.g., oral contraceptives and other steroidal agents) resulting from induction or inhibition is not anticipated, although clinical studies have not been performed.

7.12 Drugs Metabolized by CYP2C19

Results of in vitro studies demonstrate that duloxetine does not inhibit CYP2C19 activity at therapeutic

concentrations. Inhibition of the metabolism of CYP2C19 substrates is therefore not anticipated, although clinical studies have not been performed.

7.13 Monoamine Oxidase Inhibitors (MAOIs)

[See Dosage and Administration (2.5, 2.6), Contraindications (4.1), and Warnings and Precautions (5.4)].

7.14 Serotonergic Drugs

[See Dosage and Administration (2.5, 2.6), Contraindications (4.1), and Warnings and Precautions (5.4)].

7.15 Alcohol

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

In the Duloxetine Delayed-release Capsule clinical trials database, three Duloxetine Delayed-release Capsules-treated patients had liver injury as manifested by ALT and total bilirubin elevations, with evidence of obstruction. Substantial intercurrent ethanol use was present in each of these cases, and this may have contributed to the abnormalities seen [see Warnings and Precautions (5.2 and 5.11)].

7.16 CNS Drugs

[See Warnings and Precautions (5.11)].

7.17 Drugs Highly Bound to Plasma Protein

Because duloxetine is highly bound to plasma protein, administration of Duloxetine Delayed-release Capsules to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse reactions. However, co-administration of duloxetine (60 or 120 mg) with warfarin (2-9 mg), a highly protein-bound drug, did not result in significant changes in INR and in the pharmacokinetics of either total S- or total R-warfarin (protein bound plus free drug) [see Drug Interactions (7.4)].

USE IN SPECIFIC POPULATIONS SECTION

8.1 Pregnancy

Teratogenic Effects, Pregnancy Category C — 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 teratogenicity at doses up to 45 mg/kg/day (7 times the maximum recommended human dose [MRHD, 60 mg/day] and 4 times the human dose of 120 mg/day on a mg/m2 basis, in rat; 15 times the MRHD and 7 times the human dose of 120 mg/day on a mg/m2 basis in rabbit). However, fetal weights were decreased at this dose, with a no-effect dose of 10 mg/kg/day (2 times the MRHD and ≈1 times the human dose of 120 mg/day on a mg/m2 basis in rat; 3 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m2 basis 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 (5 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m2 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.

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

Nonteratogenic Effects — Neonates exposed to SSRIs or serotonin and norepinephrine reuptake

inhibitors (SNRIs), 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 features are consistent with either a direct toxic effect of SSRIs and SNRIs 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)].

When treating pregnant women with Duloxetine Delayed-release Capsules during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Duloxetine Delayed-release Capsules in the third trimester [see Dosage and Administration (2.3)].

8.2 Labor and Delivery

The effect of duloxetine on labor and delivery in humans is unknown. Duloxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

Duloxetine is excreted into the milk of lactating women. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose. Because the safety of duloxetine in infants is not known, nursing while on Duloxetine Delayed-release Capsules is not recommended. However, if the physician determines that the benefit of duloxetine therapy for the mother outweighs any potential risk to the infant, no dosage adjustment is required as lactation did not influence duloxetine pharmacokinetics.

The disposition of duloxetine was studied in 6 lactating women who were at least 12 weeks postpartum. Duloxetine 40 mg twice daily was given for 3.5 days. Like many other drugs, duloxetine is detected in breast milk, and steady state concentrations in breast milk are about one-fourth those in plasma. The amount of duloxetine in breast milk is approximately 7 µg/day while on 40 mg BID dosing. The excretion of duloxetine metabolites into breast milk was not examined. Because the safety of duloxetine in infants is not known, nursing while on Duloxetine Delayed-release Capsules is not recommended [see Dosage and Administration (2.3)].

8.4 Pediatric Use

Safety and effectiveness in the pediatric population has not been established [see Boxed Warning and Warnings and Precautions (5.1)].

Decreased appetite and weight loss have been observed in association with the use of SSRIs and SNRIs. Perform regular monitoring of weight and growth in children and adolescents treated with an SNRI such as Duloxetine Delayed-release Capsules.

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; the no-effect-level was 20 mg/kg/day.

Information describing two additional clinical studies performed by Eli Lilly and Company that failed to demonstrate pediatric efficacy is approved for Eli Lilly and Company's Duloxetine Delayed-release Capsules. However, due to Eli Lilly and Company's marketing exclusivity rights, this drug product is not labeled with that pediatric information.

8.5 Geriatric Use

Of the 2,418 patients in premarketing clinical studies of Duloxetine Delayed-release Capsules for

MDD, 5.9% (143) were 65 years of age or over. Of the 1041 patients in CLBP premarketing studies, 21.2% (221) were 65 years of age or over. Of the 487 patients in OA premarketing studies, 40.5% (197) were 65 years of age or over. Of the 1,074 patients in the DPNP premarketing studies, 33% (357) were 65 years of age or over. Premarketing clinical studies of GAD did not include sufficient numbers of subjects age 65 or over to determine whether they respond differently from younger subjects. In the MDD, DPNP, OA, and CLBP studies, no overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. SSRIs and SNRIs, including Duloxetine Delayed-release Capsules have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [see Warnings and Precautions (5.12)].

The pharmacokinetics of duloxetine after a single dose of 40 mg were compared in healthy elderly females (65 to 77 years) and healthy middle-age females (32 to 50 years). There was no difference in the Cmax, but the 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 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 patient is not necessary [see Dosage and Administration (2.3)].

8.6 Gender

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

8.7 Smoking Status

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

8.8 Race

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

8.9 Hepatic Insufficiency

Patients with clinically evident hepatic insufficiency 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). Although Cmax was similar to normals in the cirrhotic patients, the half-life was about 3 times longer [see Dosage and Administration (2.3) and Warnings and Precautions (5.13)].

8.10 Severe Renal Impairment

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, Cmax and AUC values were approximately 100% greater in patients with end-stage renal disease 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 PK analyses suggest that mild to moderate degrees of renal dysfunction (estimated CrCl 30-80 mL/min) have no significant effect on duloxetine apparent clearance [see Dosage and Administration (2.3) and Warnings and Precautions (5.13)].

DRUG ABUSE AND DEPENDENCE SECTION

9.2 Abuse

In animal studies, duloxetine did not demonstrate barbiturate-like (depressant) abuse potential.

While Duloxetine Delayed-release Capsules have not been systematically studied in humans for its potential for abuse, there was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Duloxetine Delayed-release Capsules (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

9.3 Dependence

In drug dependence studies, duloxetine did not demonstrate dependence-producing potential in rats.

OVERDOSAGE SECTION

10.1 Signs and Symptoms

In postmarketing experience, fatal outcomes have been reported for acute overdoses, primarily with mixed overdoses, but also with duloxetine only, at doses as low as 1000 mg. Signs and symptoms of overdose (duloxetine alone or with mixed drugs) included somnolence, coma, serotonin syndrome, seizures, syncope, tachycardia, hypotension, hypertension, and vomiting.

10.2 Management of Overdose

There is no specific antidote to Duloxetine Delayed-release Capsules, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. In case of acute overdose, treatment should consist of those general measures employed in the management of overdose with any drug.

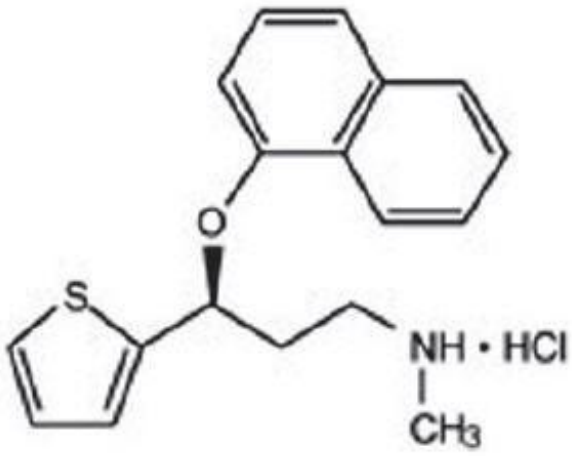
An adequate airway, oxygenation, and ventilation should be assured, and cardiac rhythm and vital signs should be monitored. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients.

Activated charcoal may be useful in limiting absorption of duloxetine from the gastrointestinal tract. Administration of activated charcoal has been shown to decrease AUC and Cmax by an average of one-third, although some subjects had a limited effect of activated charcoal. Due to the large volume of distribution of this drug, 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 are taking or have recently taken Duloxetine Delayed-release Capsules and might ingest excessive quantities of a TCA. 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) and Drug Interactions (7)]. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference (PDR).

DESCRIPTION SECTION

Duloxetine Delayed-release Capsules (duloxetine hydrochloride) are a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) for oral administration. Its chemical designation is (+)-(S)-N-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride. The empirical formula is C18H19NOS·HCl, which corresponds to a molecular weight of 333.88. The structural formula is:

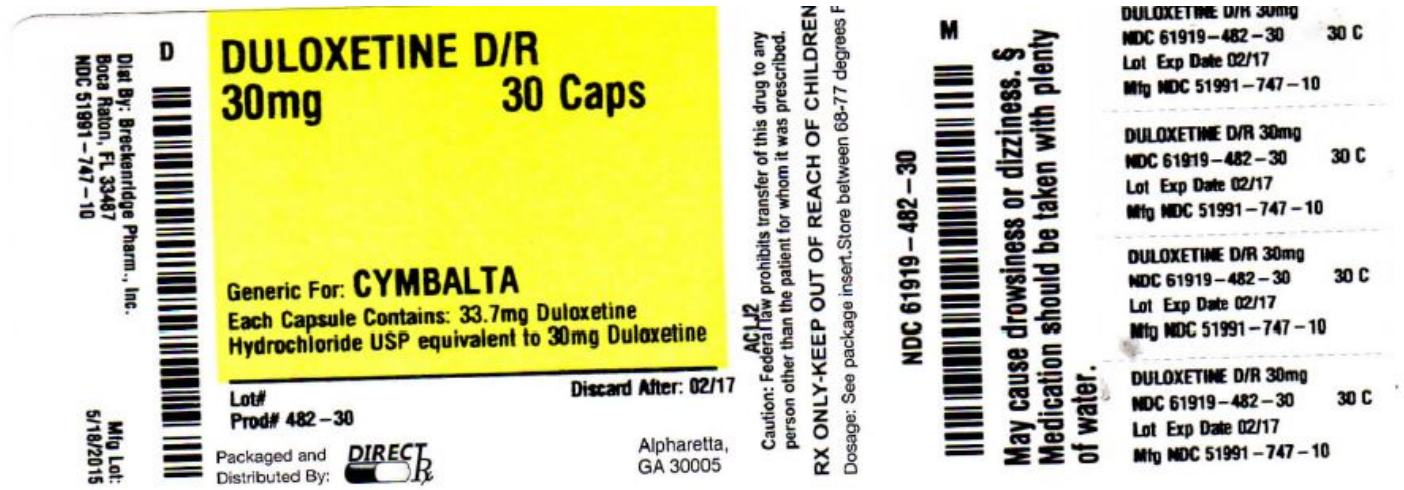


Duloxetine hydrochloride is a white to slightly brownish white solid, which is slightly soluble in water.

Each capsule contains enteric-coated pellets of 22.4, 33.7, or 67.3 mg of duloxetine hydrochloride equivalent to 20, 30, or 60 mg of duloxetine, respectively. These enteric-coated pellets are designed to prevent degradation of the drug in the acidic environment of the stomach. Inactive ingredients include ammonium hydroxide, black iron oxide, hypromellose, methacrylic acid copolymer dispersion (methacrylic acid-ethyl acrylate copolymer, polysorbate 80, sodium lauryl sulfate), potassium hydroxide, propylene glycol, shellac, sucrose, sugar spheres (maize starch, sucrose), talc, titanium dioxide, triethylcitrate, and hard gelatin capsules (gelatin, titanium dioxide). The 20 mg hard gelatin capsule colorant is yellow iron oxide. The 30 mg hard gelatin capsule colorants are FD&C Blue No. 1, FD&C Yellow No. 6, and FD&C Yellow No. 10. The 60 mg hard gelatin capsule colorants are FD&C Blue No. 1, FD&C Yellow No. 6, FD&C Yellow No.10, and yellow iron oxide.

Close

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL



DULOXETINE HYDROCHLORIDE

duloxetine hydrochloride capsule, delayed release pellets

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:61919-482(NDC:51991-747)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
DULOXETINE HYDROCHLORIDE (UNII: 9044SC542W) (DULOXETINE - UNII:O5TNM5N07U)	DULOXETINE	30 mg

Inactive Ingredients	
Ingredient Name	**Strength**
HYPROMELLOSES (UNII: 3NXW29V3WO)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
METHACRYLIC ACID - ETHYL ACRYLATE COPOLYMER (1:1) TYPE A (UNII: NX76LV5T8J)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
TRIETHYL CITRATE (UNII: 8Z96QXD6UM)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
AMMONIA (UNII: 5138Q19F1X)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
SHELLAC (UNII: 46N107B71O)	
SUCROSE (UNII: C151H8M554)	
STARCH, CORN (UNII: O8232NY3SJ)	
GELATIN (UNII: 2G86QN327L)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	

Product Characteristics			
Color	green (WHITE) , white	**Score**	no score
Shape	CAPSULE	**Size**	16mm
Flavor		**Imprint Code**	B;747
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:61919-482-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	05/19/2015	
2	NDC:61919-482-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	05/19/2015	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA203088	01/01/2014	

Labeler - DIRECT RX (079254320)

Establishment

Name	Address	ID/FEI	Business Operations
DIRECT RX		079254320	relabel(61919-482) , repack(61919-482)

Revised: 7/2016

DIRECT RX