Size: 450 x 800 mm
Folds: Folding: 38 x 38 mm
Colour: Pantone Black C
Note: Printed on 28 GSM Bible paper, front & back side printing.
Note: Pharma code position and Orientation are tentative, will be change based on folding size
Note: 2D Barcode to be overprinting at supplier end & it contains our item code, supplier serial number.

170-2021-10

Duloxetine Delayed-Release Capsules, USP

2065284

Space for 2D Code

Medication Guide

Duloxetine Delayed-Release Capsules, USP
(doo lox'e teen)

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

Talk to your healthcare provider about:

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

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

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

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

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

What else do I need to know about antidepressant medicines?

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

What are duloxetine delayed-release capsules?

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

Duloxetine delayed-release capsules are also used to treat or manage:

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

Who should not take duloxetine delayed-release capsules?

Do Not take duloxetine delayed-release capsules if you:

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

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

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

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

- have heart problems or high blood pressure
- have diabetes (Duloxetine delayed-release capsules treatment makes it harder for some people with diabetes to control their blood sugar)
- have liver problems
- have kidney problems
- have glaucoma
- have or had seizures or convulsions
- have bipolar disorder or mania
- have low sodium levels in your blood
- have delayed stomach emptying
- have or had bleeding problems
- are pregnant or plan to become pregnant. Duloxetine delayed-release capsules may harm your unborn baby. Talk to your healthcare provider about the risk to your unborn baby if you take duloxetine delayed-release capsules during pregnancy.
  - Tell your healthcare provider right away if you become pregnant or think you are pregnant during treatment with duloxetine delayed-release capsules.
- are breastfeeding or plan to breastfeed. Duloxetine passes into your breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby while taking duloxetine delayed-release capsules.

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

Especially tell your healthcare provider if you take:

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

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

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

How should I take duloxetine delayed-release capsules?

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

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

- Duloxetine delayed-release capsules can cause sleepiness or may affect your ability to make decisions, think clearly, or react quickly. You should not drive, operate heavy machinery, or do other dangerous activities until you know how duloxetine delayed-release capsules affect you.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DULOXETINE DELAYED-RELEASE CAPSULES safely and effectively. See full prescribing information for DULOXETINE DELAYED-RELEASE CAPSULES.
DULOXETINE delayed-release capsules, for oral use
Initial U.S. Approval: 2004

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.

- **Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for major depressive disorder (MDD) and other indications.**
- **Monitor for worsening and emergence of suicidal thoughts and behaviors (5.1)**

RECENT MAJOR CHANGES 07/2021
Warnings and Precautions (5.5) Hepatotoxicity, Liver Failure and Acute Liver Injury

INDICATIONS AND USAGE
Major depressive disorder (MDD) in adults (1)
Diabetic peripheral neuropathic pain (DPNP) in adults (1)
Chronic musculoskeletal pain (1)
Generalized anxiety disorder (GAD) in adults (1)
Limitations of use: Not studied in combination with other MAOIs (1)

DOSAGE AND ADMINISTRATION
Indicated for the treatment of the following conditions:
Major depressive disorder (MDD) in adults (2)
Diabetic peripheral neuropathic pain (DPNP) in adults (2)
Chronic musculoskeletal pain (2)
Generalized anxiety disorder (GAD) in adults (2)
Usual dosage range: 60 mg once daily or 30 mg twice daily. Sensitive adults, or those taking CYP1A2 inhibitors, may begin at 30 mg once daily and increase to 60 mg once daily if needed (2)

DOSAGE FORMS AND STRENGTHS
Delayed-release capsules: 20 mg, 30 mg, and 60 mg (3)

CONTRAINDICATIONS
Concomitant use of an MAOI and within 5 days after stopping duloxetine delayed-release capsules are contraindicated
In combination with or within 14 days of stopping an MAOI antidepressant or serotonin receptor agonist (for migraine or serotonin syndrome)
Hepatic impairment
Uncontrolled narrow-angle glaucoma
Hypersensitivity to duloxetine delayed-release capsules or to other duloxetine products
Concomitant use in patients taking potent inhibitors of CYP1A2 and who have liver disease
Concomitant use in patients taking fluvoxamine
Concomitant use in patients taking thioridazine (5)

WARNINGS AND PRECAUTIONS
Serotonin Syndrome: Discontinue duloxetine delayed-release capsules if syndrome is suspected (5.2)
Activation of mania/hypomania: Use with caution in patients with a history of mania (5.3)
Increased risk of bleeding: Concomitant use of duloxetine delayed-release capsules with NSAIDs, aspirin, and warfarin may increase the risk of bleeding events (5.4)
Severe skin reactions: Discontinue duloxetine delayed-release capsules at the first sign of rash or other skin reactions (5.6)
Hepatotoxicity: Do not use duloxetine delayed-release capsules in patients with liver disease (5.7)
Elevation of blood pressure: Monitor blood pressure (5.8)
Withdrawal reactions: Gradually reduce dose rather than abruptly discontinue whenever possible (5.9)
Hyponatremia: Consider discontinuing duloxetine delayed-release capsules in patients with symptomatic hyponatremia (5.10)
Urinary hesitation and retention: Use with caution in patients with these symptoms (5.11)
Increased risk of bleeding: May increase the risk of bleeding events. Concomitant use of aspirin and NSAIDs may increase the risk of gastrointestinal bleeding (5.12)
Eosinophilic pneumonia: Discontinue duloxetine delayed-release capsules in patients with suspected eosinophilic pneumonia (5.13)
Serotonin syndrome: Increased risk when co-administered with other serotonergic agents (e.g. triptans, tramadol, SSRIs, SNRIs, lithium, tryptophan, and St. John's Wort), and with drugs that impair metabolism of serotonin (e.g. MAOIs, CYP2D6 inhibitors) (5.2, 7.2)
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, somnolence/sedation, decreased appetite, insomnia, constipation, and hyperhidrosis
Pediatric Patients: decreased weight, decreased appetite, insomnia, vomiting, fatigue and dizziness
To report SUSPECTED ADVERSE REACTIONS, contact Nobex Labs Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.
Revised: 10/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Important Administration Instructions
2.2 Dosage for Treatment of Major Depressive Disorder in Adults
2.3 Dosage for Treatment of Generalized Anxiety Disorder
2.4 Dosage for Treatment of Diabetic Peripheral Neuropathic Pain in Adults
2.5 Dosage for Treatment of Chronic Musculoskeletal Pain in Adults
2.6 Dosage for Treatment of Fibromyalgia
2.7 Dosage for Treatment of Chronic Musculoskeletal Pain in Adolescents
2.8 Dosage for Treatment of Major Depressive Disorder in Pediatric Patients
2.9 Switching a Patient to or from a Monoamine Oxidase Inhibitor (MAOI) Intended for Treatment of Psychiatric Disorders
2.10 Use of Duloxetine Delayed-Release Capsules with Other MAOIs such as Linezolid or Methylene Blue
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults
5.2 Serotonin Syndrome
5.3 Activation of Mania/Hypomania
5.4 Increased Risk of Bleeding
5.5 Hepatotoxicity and Liver Injury
5.6 Severe Skin Reactions
5.7 Elevation of Blood Pressure
5.8 Withdrawal Reactions
5.9 Activation of Mania/Hypomania
5.10 Hyponatremia
5.11 Urinary Hesitation and Retention
5.12 Eosinophilic Pneumonia
5.13 Sexual Dysfunction
5.14 Liver Injury and Elevation of Transaminases
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Inhibitors of CYP1A2
7.2 Inhibitors of CYP2D6
7.3 Inhibitors of CYP2C19 and CYP2D6
7.4 Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)
7.5 Serotonergic Drugs
7.6 Drugs that Prolong QT Interval
7.7 Drugs that Affect Gastric Acidity
7.8 Drugs Metabolized by CYP1A2
7.9 Drugs Metabolized by CYP2D6
7.10 Drugs Metabolized by CYP2C19
7.11 Drugs Highly Bound to Plasma Protein
7.12 Drugs Metabolized by CYP2D6, CYP2C19 and Other Routes of Elimination (MAOIs)
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Hepatic Impairment
8.7 Renal Impairment
8.8 Smoking Status
8.9 Race
10 DRUG ABUSE AND DEPENDENCE
10.1 Controlled Substance
10.2 Abuse
10.3 Dependence
10 OVERDOSAGE
10.1 Human Experience
10.2 Management of Acute Overdose
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Major Depressive Disorder in Adults
14.2 Diabetic Peripheral Neuropathic Pain in Adults
14.3 Chronic Musculoskeletal Pain in Adults
14.4 Generalized Anxiety Disorder in Adults
14.5 Chronic Musculoskeletal Pain in Adolescents
15 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Storage and Handling
17 PATIENT COUNSELING INFORMATION
*Sections or subsections omitted from the full prescribing information are not listed.

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies. These 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 in risk with antidepressants in patients aged 65 and older (see Warnings and Precautions).

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).

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

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

- Major depressive disorder in adults
- Diabetic peripheral neuropathic pain in adults
- Chronic musculoskeletal pain in adults
- Generalized anxiety disorder in adults

Pharmacoepidemiologic studies have shown that major depressive disorder (MDD) and other psychiatric disorders are associated with increased risk of suicide. Epidemiologic studies have also shown that treatment with antidepressants may increase the risk of suicide in some patients. Patients with major depressive disorder (MDD) or other psychiatric disorders may also be at increased risk for suicide regardless of their treatment status. The risk of suicide should be considered in these patients before beginning treatment with any antidepressant, including duloxetine delayed-release capsules, and throughout treatment. The lowest dosage should be used in order to minimize the risk of overdose from suicide attempts. Prescriptions for duloxetine delayed-release capsules should be written for the smallest quantity of duloxetine delayed-release capsules consistent with good patient management, in order to reduce the risk of overdosage.

Screening patients for bipolar disorder, including a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression, should be performed prior to initiating treatment with an antidepressant medication. Duloxetine delayed-release capsules are not approved for the treatment of bipolar disorder. Duloxetine delayed-release capsules should be used with caution in patients with a history of mania or hypomania.

Duloxetine delayed-release capsules are not approved for the treatment of pediatric MDD. Safety and effectiveness in the treatment of other psychiatric disorders in pediatric patients have not been established for any other indication than pediatric diabetic peripheral neuropathy (see Warnings and Precautions).

2. DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

Take duloxetine delayed-release capsules once daily or twice daily (depending on the indication) with or without food. Duloxetine delayed-release capsules should be swallowed whole. Do not open the capsule and sprinkle on food or mix with liquids. Opening the capsule may affect how well duloxetine delayed-release capsules works.

2.2 Dosage for Treatment of Major Depressive Disorder in Adults

The recommended dose for duloxetine delayed-release capsules treatment of MDD is 60 mg once daily. Doses of 120 mg per day were studied in a controlled trial and were not more effective than 60 mg per day. Some patients who do not respond to a 60 mg per day dose may respond to a higher dose. Duloxetine delayed-release capsules should be taken with a total daily dose of 60 mg or 120 mg.

2.3 Dosage for Treatment of Generalized Anxiety Disorder

The recommended dose for duloxetine delayed-release capsules treatment of GAD is 60 mg once daily. Some patients who do not respond to a 60 mg per day dose may respond to a higher dose. Duloxetine delayed-release capsules should be taken with a total daily dose of 60 mg or 120 mg.

2.4 Dosage for Treatment of Diabetic Peripheral Neuropathic Pain in Adults

The recommended dose for duloxetine delayed-release capsules treatment of DPNP is 60 mg once daily. Duloxetine delayed-release capsules should be taken with a total daily dose of 60 mg or 120 mg.

Pharmacokinetic data suggest that plasma duloxetine exposure is greater in some patients with DPNP than in healthy subjects or patients with MDD. Slower titration and a lower maintenance dose may improve the tolerability of duloxetine delayed-release capsules in some patients.

2.5 Dosage for Treatment of Chronic Musculoskeletal Pain in Adults

The recommended dose for duloxetine delayed-release capsules treatment of chronic musculoskeletal pain is 60 mg once daily. Doses of 120 mg per day were studied in a controlled trial and were not more effective than 60 mg per day. Some patients who do not respond to a 60 mg per day dose may respond to a higher dose. Duloxetine delayed-release capsules should be taken with a total daily dose of 60 mg or 120 mg.

Chronic musculoskeletal pain is a heterogeneous category of pain. Duloxetine delayed-release capsules have been studied in patients with chronic musculoskeletal pain of the lower back, hip, and knee of mixed etiology, chronic musculoskeletal pain of the lower back of presumed osteoarthritis etiology, and chronic musculoskeletal pain of the lower back of presumed chronic nonspecific etiology. Pharmacokinetic data suggest that plasma duloxetine exposure is greater in some patients with chronic musculoskeletal pain than in healthy subjects or patients with MDD. Slower titration and a lower maintenance dose may improve the tolerability of duloxetine delayed-release capsules in some patients.

2.6 Dosage for Treatment of Fibromyalgia

The recommended dose for duloxetine delayed-release capsules treatment of fibromyalgia is 60 mg once daily. Doses of 120 mg per day were studied in a controlled trial and were not more effective than 60 mg per day. Some patients who do not respond to a 60 mg per day dose may respond to a higher dose. Duloxetine delayed-release capsules should be taken with a total daily dose of 60 mg or 120 mg.

Pharmacokinetic data suggest that plasma duloxetine exposure is greater in some patients with fibromyalgia than in healthy subjects or patients with MDD. Slower titration and a lower maintenance dose may improve the tolerability of duloxetine delayed-release capsules in some patients.

2.7 Dosage in Patients with Hepatic Impairment or Severe Renal Impairment

Use of duloxetine delayed-release capsules in patients with chronic liver disease is contraindicated (see Use in Specific Populations 8.6).

Use of duloxetine delayed-release capsules in patients with severe renal impairment (see Dosage and Administration 2.7) is not recommended.

2.8 Dosage in Pediatric Patients with Major Depressive Disorder

Recommended Dosage in Pediatric Patients

The recommended dose for duloxetine delayed-release capsules treatment of MDD in pediatric patients 7 years of age and older is 30 mg once daily for 2 weeks, then increase to the recommended dose of 60 mg once daily. The maximum dose studied in controlled clinical trials was 60 mg per day. Some patients who do not respond to a 60 mg per day dose may respond to a higher dose. The maximum dose evaluated in these clinical trials was 120 mg per day.

Pharmacokinetic data suggest that plasma duloxetine exposure is greater in pediatric patients than in adults. Slower titration and a lower maintenance dose may improve the tolerability of duloxetine delayed-release capsules in some patients.

Duloxetine delayed-release capsules are not approved for the treatment of pediatric MDD in patients 7 years of age and younger.

2.9 Switching a Patient to or from a Monoamine Oxidase Inhibitor (MAOI) Intended for Treatment of Psychiatric Disorders

At least 14 days should elapse between the discontinuation of a MAOI intended for treatment of psychiatric disorders and initiation of duloxetine delayed-release capsules. Conversely, at least 14 days should be allowed after stopping duloxetine delayed-release capsules before starting an MAOI intended for treatment of psychiatric disorders.

In addition, duloxetine delayed-release capsules should be used cautiously in patients receiving other centrally acting drugs with serotonin reuptake inhibition or monoamine neurotransmitter uptake inhibition properties (see Warnings and Precautions 5.2).

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

Starting duloxetine delayed-release capsules in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is contraindicated because there is an increased risk of serotonin syndrome in such patients.

In a study in healthy adult volunteers, administration of linezolid, an antibiotic and a reversible, non-selective MAOI, to patients taking duloxetine delayed-release capsules was associated with blood pressure elevation and central nervous system disorders such as dizziness and hyperreflexia. The administration of methylene blue, a parenteral MAOI, to patients taking duloxetine delayed-release capsules may also be associated with the development of serotonin syndrome and blood pressure elevation. Because the duration of interaction following administration of linezolid or methylene blue is unknown, duloxetine delayed-release capsules should be withheld for at least 14 days after administration of linezolid or methylene blue, unless the patient's condition warrants urgent treatment with linezolid. The administration of linezolid or methylene blue should be considered for patients who have taken duloxetine delayed-release capsules within 14 days of stopping treatment with duloxetine delayed-release capsules. Serotonin syndrome may occur after discontinuation of duloxetine delayed-release capsules (see Warnings and Precautions 5.2).

The use of duloxetine delayed-release capsules in combination with linezolid or methylene blue is contraindicated because the risk of serotonin syndrome has not been evaluated in this combination. The use of duloxetine delayed-release capsules in combination with other MAOIs is contraindicated because the risk of serotonin syndrome has been reported with such combinations. Starting duloxetine delayed-release capsules in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is contraindicated (see Contraindications 4).

3. DOSAGE FORMS AND STRENGTHS

Delayed-release capsules: 20 mg, 30 mg, and 60 mg (3).

4. CONTRAINDICATIONS

- Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) intended to treat psychiatric disorders and within 5 days after stopping duloxetine delayed-release capsules treatment of patients taking MAOIs intended to treat psychiatric disorders (2.9, 2.10, 5.2, 7.1)
- Concomitant use in patients taking potent inhibitors of CYP1A2 and who have liver disease (7.1, 7.8)
- Concomitant use in patients taking fluvoxamine (7.1, 7.8)
- Hepatic impairment (8.6)
- Uncontrolled narrow-angle glaucoma (7.4)
- Hypersensitivity to duloxetine delayed-release capsules or to other duloxetine products (10.3)
- Concomitant use in patients taking thioridazine (5.12, 7.6)

5. WARNINGS AND PRECAUTIONS

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

Patients who take antidepressant medicines for any indication may be at increased risk for suicidal thinking and behavior (suicidality) and should be closely monitored for clinical worsening, suicidality, and unusual changes in behavior when starting treatment with an antidepressant medicine and during dose adjustments. Anyone who is considering the use of an antidepressant medicine must balance the potential risk of treatment against the need for such treatment in each patient, taking into account the patient's medical condition and other factors that lead to the decision to prescribe an antidepressant medicine. Depression and certain other psychiatric disorders are themselves associated with increased risk of suicidal thinking and behavior and should be treated appropriately. Patients of all ages who are prescribed an antidepressant should be adequately observed 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.

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

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

Pooled analyses of 295 short-term placebo-controlled trials of antidepressants (SSRIs and other antidepressants) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 subjects who took antidepressants and attempted suicide. No suicide attempt was recorded in the placebo-treated patients, but the number of suicide attempts was too small to allow any conclusion about drug effect on suicidality.

It is unknown if the observed increased risk of suicidality in clinical trials extends to patients who take antidepressants for other indications, such as obsessive compulsive disorder (OCD) or other psychiatric disorders included in this paragraph, but the same cautions apply to prescriptions for these other indications. Although there is a wide spectrum of severity and type of psychiatric illness among those who were studied in clinical trials of antidepressant drugs, the increased risk of suicidality observed in children, adolescents, and young adults taking antidepressants must be considered when deciding to prescribe any form of antidepressant medication.

Monitoring and close observation should accompany the initiation of all antidepressant medications. The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder (MDD) and other indications, both psychiatric and nonpsychiatric. Although a causal relationship between the emergence of such symptoms and either the pharmacotherapy of depression or the emergence of suicidal impulses has not been established, there is concern that such symptoms may precede the emergence of suicidal ideation or behavior in patients at risk for suicide, and should be carefully monitored and considered in the management of depression. Families and caregivers should be advised of the need for close observation and communication with the prescriber, and should be cautioned about the potential emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, in addition to the emergence of suicidal ideation and behavior, which may be the most serious consequence of such symptoms.

Prescriptions for duloxetine delayed-release capsules should be written for the smallest quantity of duloxetine delayed-release capsules consistent with good patient management, in order to reduce the risk of overdosage.

Screening patients for bipolar disorder, including a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression, should be performed prior to initiating treatment with an antidepressant medication. Duloxetine delayed-release capsules are not approved for the treatment of bipolar disorder. Duloxetine delayed-release capsules should be used with caution in patients with a history of mania or hypomania.

Duloxetine delayed-release capsules are not approved for the treatment of pediatric MDD. Safety and effectiveness in the treatment of other psychiatric disorders in pediatric patients have not been established for any other indication than pediatric diabetic peripheral neuropathy (see Warnings and Precautions).

5.2 Serotonin Syndrome

Serotonin Syndrome: Discontinue duloxetine delayed-release capsules if syndrome is suspected (5.2)

Serotonin Syndrome: Increased risk when co-administered with other serotonergic agents (e.g. triptans, tramadol, SSRIs, SNRIs, lithium, tryptophan, and St. John's Wort), and with drugs that impair metabolism of serotonin (e.g. MAOIs, CYP2D6 inhibitors) (5.2, 7.2)

Serotonin Syndrome: Duloxetine delayed-release capsules may cause symptoms of sexual dysfunction (5.15)

Increased Risk of Bleeding: May increase the risk of bleeding events. Concomitant use of aspirin and NSAIDs may increase the risk of gastrointestinal bleeding (5.12)

Severe Skin Reactions: Severe skin reactions, including erythema multiforme and Stevens-Johnson Syndrome, have been taken since the approval. Discontinue duloxetine delayed-release capsules at the first sign of rash or other skin reactions (5.6)

Activation of mania/hypomania: Use with caution in patients with a history of mania/hypomania, a history of bipolar disorder, mania, or hypomania (5.9)

Hepatotoxicity: Do not use duloxetine delayed-release capsules in patients with liver disease (5.7)

Elevation of blood pressure: Monitor blood pressure in patients treated with duloxetine delayed-release capsules (5.8)

Withdrawal reactions: Gradually reduce dose rather than abruptly discontinue whenever possible (5.9)

Hyponatremia: Consider discontinuing duloxetine delayed-release capsules in patients with symptomatic hyponatremia (5.10)

Urinary hesitation and retention: Use with caution in patients with these symptoms (5.11)

Eosinophilic pneumonia: Discontinue duloxetine delayed-release capsules in patients with suspected eosinophilic pneumonia (5.13)

Sexual Dysfunction: Duloxetine delayed-release capsules may cause symptoms of sexual dysfunction (5.15)

Serotonin Syndrome: Serotonin Syndrome has been reported with duloxetine delayed-release capsules, particularly when given in combination with other serotonergic agents (including SSRIs, SNRIs, tryptophan, triptans, tricyclics, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's Wort), and with drugs that impair metabolism of serotonin (including MAOIs, CYP2D6 inhibitors). Serotonin Syndrome may be life threatening. The risk of serotonin syndrome may be increased when duloxetine delayed-release capsules are used in combination with other serotonergic agents, and should be carefully monitored when initiating or increasing the dose of these agents. Discontinuation of duloxetine delayed-release capsules and other serotonergic agents should be considered if patients report new or worsening symptoms that are consistent with serotonin syndrome. Symptoms may include changes in mental status (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

Concomitant use of duloxetine delayed-release capsules with MAOI antidepressants is contraindicated. At least 14 days should elapse between the discontinuation of a MAOI intended for treatment of psychiatric disorders and initiation of duloxetine delayed-release capsules. Conversely, at least 14 days should be allowed after stopping duloxetine delayed-release capsules before starting an MAOI intended for treatment of psychiatric disorders. In addition, duloxetine delayed-release capsules should be used cautiously in patients receiving other centrally acting drugs with serotonin reuptake inhibition or monoamine neurotransmitter uptake inhibition properties (see Warnings and Precautions 5.2).

Serotonin Syndrome in Combination with Other MAOIs such as Linezolid or Methylene Blue: Serotonin Syndrome has been reported with MAOIs, and combination of a MAOI and duloxetine delayed-release capsules is contraindicated. Starting duloxetine delayed-release capsules in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is contraindicated because there is an increased risk of serotonin syndrome in such patients.

In a study in healthy adult volunteers, administration of linezolid, an antibiotic and a reversible, non-selective MAOI, to patients taking duloxetine delayed-release capsules was associated with blood pressure elevation and central nervous system disorders such as dizziness and hyperreflexia. The administration of methylene blue, a parenteral MAOI, to patients taking duloxetine delayed-release capsules may also be associated with the development of serotonin syndrome and blood pressure elevation. Because the duration of interaction following administration of linezolid or methylene blue is unknown, duloxetine delayed-release capsules should be withheld for at least 14 days after administration of linezolid or methylene blue, unless the patient's condition warrants urgent treatment with linezolid. The administration of linezolid or methylene blue should be considered for patients who have taken duloxetine delayed-release capsules within 14 days of stopping treatment with duloxetine delayed-release capsules. Serotonin Syndrome may occur after discontinuation of duloxetine delayed-release capsules (see Warnings and Precautions 5.2).

The use of duloxetine delayed-release capsules in combination with linezolid or methylene blue is contraindicated because the risk of serotonin syndrome has not been evaluated in this combination. The use of duloxetine delayed-release capsules in combination with other MAOIs is contraindicated because the risk of serotonin syndrome has been reported with such combinations. Starting duloxetine delayed-release capsules in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is contraindicated because there is an increased risk of serotonin syndrome in such patients.

5.3 Activation of Mania/Hypomania

Activation of mania/hypomania has been reported in a small proportion of patients with mood disorders who have been treated with antidepressant drugs. Sufficient experience was not obtained in clinical trials to determine whether or to what extent the risk of activation of mania/hypomania may be increased by the administration of duloxetine delayed-release capsules in patients with a history of mania/hypomania. Use with caution in patients with a history of mania/hypomania.

5.4 Increased Risk of Bleeding

Duloxetine delayed-release capsules may increase the risk of bleeding events. Concomitant use of aspirin and NSAIDs may increase the risk of gastrointestinal bleeding (see Warnings and Precautions 5.12).

Drugs that interfere with hemostasis (for example, NSAIDs, aspirin, and warfarin) may increase the risk of bleeding-related adverse events in patients who have been treated with duloxetine delayed-release capsules. The concomitant use of duloxetine delayed-release capsules and warfarin in stable coumarin anticoagulant patients may be associated with bleeding events or with changes in prothrombin time, all of which were serious in some patients. Bleeding events have been reported following the concomitant use of duloxetine delayed-release capsules and NSAIDs, aspirin, or other drugs that affect coagulation (see Drug Interactions 7.4).

Bleeding events have been reported in patients taking anticoagulants and/or platelet inhibitors in addition to duloxetine delayed-release capsules. The bleeding events ranged in severity from ecchymosis, hematoma, and epistaxis to life-threatening hemorrhage. The use of duloxetine delayed-release capsules may increase the risk of bleeding events associated with the use of these other drugs. Consideration should be given to the risk of bleeding events associated with the concomitant use of duloxetine delayed-release capsules and platelet inhibitors and anticoagulants.

5.5 Hepatotoxicity and Liver Injury

Duloxetine delayed-release capsules are not recommended for patients with liver disease. Duloxetine delayed-release capsules have been associated with liver injury and elevation of transaminases.

Cases of hepatic failure have been reported in patients taking duloxetine delayed-release capsules. These cases have been reported in patients who have been taking duloxetine delayed-release capsules for more than one year, but they have also been reported in patients who have been taking duloxetine delayed-release capsules for a shorter period of time. Most of these cases have been in women. Although these cases do not provide a clear estimate of the incidence of hepatic failure associated with duloxetine delayed-release capsules, the reported cases do suggest the possibility of severe liver dysfunction in patients who have been treated with duloxetine delayed-release capsules for a short period of time.

Elevations of transaminase levels to greater than 10 times the upper limit of normal have been reported in clinical trials with duloxetine delayed-release capsules. In the majority of

In studies up to 9 months, duloxetine delayed-release capsules treated patients experienced nausea (reported as a side effect by 21% of patients treated with duloxetine delayed-release capsules versus 10% in placebo-treated patients), dry mouth (reported by 13% versus 5%), increased sweating (reported by 11% versus 3%), decreased appetite (reported by 11% versus 2%), and constipation (reported by 10% versus 3%). Nausea was observed during the first week of treatment, was generally transient, and was most frequently reported during the first two weeks of treatment. In a long-term (52 weeks) study in patients who had responded to duloxetine delayed-release capsules during a 26-week open-label phase followed by a 26-week double-blind, placebo-controlled phase, the incidence of nausea was similar in patients who continued on duloxetine delayed-release capsules (9%) versus those who were switched to placebo (8%).

Additionally, the benefit of treatment with duloxetine delayed-release capsules at 60 mg/day was evaluated in a separate trial (Study PBR-3). Adult patients were enrolled, treated with duloxetine delayed-release capsules 60 mg/day for 6 weeks, followed by 2 weeks of placebo, and then treated with duloxetine delayed-release capsules 60 mg/day for 6 weeks. The incidence of nausea was 19% during the first 6 weeks of treatment, 5% during the 2-week placebo period, and 7% during the second 6-week period of treatment with duloxetine delayed-release capsules 60 mg.

Percent Improvement in Pain from Baseline

Figure 6: Percentage of Adult Fibromyalgia Patients Achieving Various Levels of Pain Relief at Study Endpoint as Measured by 24-Hour Average Pain Severity (Study FM-1)

Figure 7: Percentage of Adult Patients with GAD Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study GAD-1)

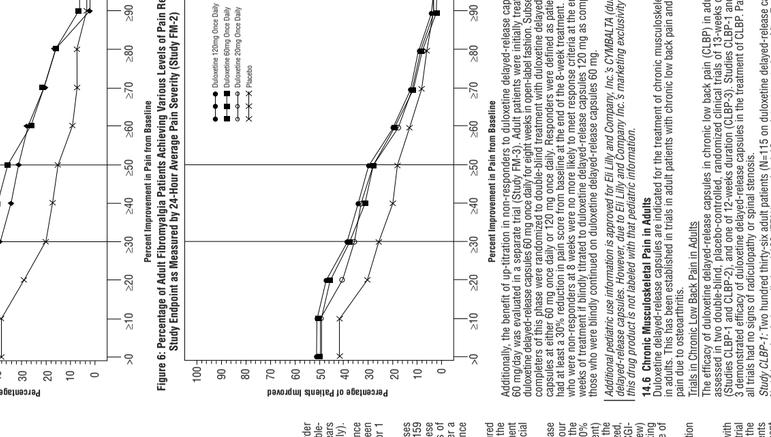

Figure 8: Percentage of Adult Patients with GAD Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study GAD-2)

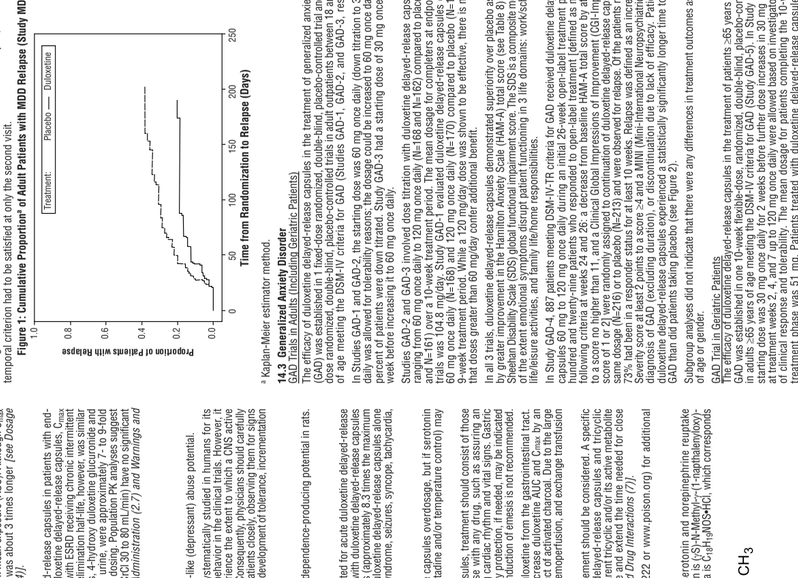

Figure 9: Percentage of Adult Patients with GP Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study CLEP-3)

Figure 10: Percentage of Adult Patients with GA Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study GA-1)

Figure 11: Percentage of Adult Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study GA-2)

Figure 12: Percentage of Adult Patients with GA Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study GA-3)

Figure 13: Percentage of Adult Patients with CLBP Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study CLBP-3)

Figure 14: Percentage of Adult Patients with OA Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study OA-1)

Figure 15: Percentage of Adult Patients with OA Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study OA-2)

Figure 16: Percentage of Adult Patients with OA Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study OA-3)

Figure 17: Percentage of Adult Patients with OA Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study OA-4)

Figure 18: Percentage of Adult Patients with CLBP Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study CLBP-4)

Figure 19: Percentage of Adult Patients with CIPN Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study CIPN-1)

Figure 20: Percentage of Adult Patients with OP Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study CLEP-2)

Figure 21: Percentage of Adult Patients with SUI Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study SUI-1)

Figure 22: Percentage of Adult Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study UI-1)

Figure 23: Percentage of Adult Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study UI-2)

Figure 24: Percentage of Adult Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study UI-3)

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

5.2 Pulmonary/Allergic

In the MDD, GAD, DPNP, FM, OA, and CLBP studies, no overall differences in safety or effectiveness were observed in subjects taking duloxetine delayed-release capsules and elderly subjects (≥65 years) given the small sample size and the heterogeneous nature of the patient population. Elderly patients may be at greater risk for some adverse reactions (*see Warnings and Precautions (5.8)*).

Studies FM-1 and FM-2 compared duloxetine delayed-release capsules 60 mg once daily or 120 mg once daily administered as a fixed dose, with placebo in adult patients with fibromyalgia (*see Clinical Studies*). Study FM-1 additionally compared duloxetine delayed-release capsules 20 mg with placebo among patients who were intolerant to 60 mg.

Treatment with duloxetine delayed-release capsules 60 mg or 120 mg daily statistically significantly improved the mean pain score in females, but not in males, as compared to placebo in the combined analysis of these two fibromyalgia studies. Data from male patients were insufficient to support a finding of effectiveness in this population. The figures and corresponding tables include data from both male and female patients. The figure and corresponding table for the primary efficacy variable in the pooled female patient population from these two studies follow. Treatment with duloxetine delayed-release capsules 20 mg was not statistically superior to placebo.

Table 5: Summary of the Primary Efficacy Results for Adult Trials in MDD

Study Number	Treatment Group	Primary Efficacy Measure: HAMD-17	
		Mean Baseline Score (SD)	Placebo-adjusted Mean Change from Baseline (95% CI)
Study MDD-1	Duloxetine Delayed-Release Capsules 60 mg/day[a]	21.5 (4.10)	-10.9 (0.70)
	Duloxetine Delayed-Release Capsules 120 mg/day[a]	21.1 (3.71)	-6.1 (0.69)
	Placebo	21.3 (3.82)	–
Study MDD-2	Duloxetine Delayed-Release Capsules 60 mg/day[a]	20.3 (3.32)	-10.5 (0.71)
	Duloxetine Delayed-Release Capsules 120 mg/day[a]	20.3 (3.42)	-8.3 (0.67)
	Placebo	19.8 (3.58)	-2.4 (-4.7, -0.2)
Study MDD-3	Duloxetine Delayed-Release Capsules 20 mg/day[a]	17.2 (5.11)	-5.0 (0.81)
	Duloxetine Delayed-Release Capsules 60 mg/day[a]	18.1 (4.52)	-3.6 (-5.9, -1.4)
	Placebo	19.9 (3.54)	-11.0 (0.49)
Study MDD-4	Duloxetine Delayed-Release Capsules 60 mg/day[a]	20.2 (3.41)	-12.1 (0.49)
	Duloxetine Delayed-Release Capsules 120 mg/day[a]	19.9 (3.58)	-8.8 (0.50)
	Placebo	20.1 (3.58)	-8.8 (0.50)

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval; not groups were included.

[a] Statistically significant vs placebo.

least-squares mean; CI: confidence interval; not groups were included.

[a] Statistically significant vs placebo.

5.7 Urinary

Criteria for MDD received duloxetine delayed-release capsules 40 mg once daily with fluoxetine 20 mg, a fixed dose combination of duloxetine delayed-release capsules and fluoxetine, or placebo for 8 weeks. Patients who had a partial response to fluoxetine alone were randomized to continuation of fluoxetine 20 mg or to the fixed dose combination of duloxetine delayed-release capsules and fluoxetine. The fixed dose combination of duloxetine delayed-release capsules and fluoxetine was statistically significantly superior to fluoxetine 20 mg in the primary efficacy variable, the change from baseline to the last visit on the Clinical Global Impressions-Depression Improvement (CGI-I) scale (see Table 6). The fixed dose combination of duloxetine delayed-release capsules and fluoxetine was also superior to fluoxetine 20 mg on the 17-item Hamilton Depression Rating Scale (HAMD-17) total score, the HAMD-17 Depressed Mood factor score, the HAMD-17 Anxiety factor score, and the Sheehan Disability Scale total score. The figures and corresponding tables below display the results for the primary efficacy variable and the HAMD-17 total score for this study.

Table 6: Summary of the Primary Efficacy Results for Adult Trials in MDD Patients with Partial Response to Fluoxetine

Treatment Group	Primary Efficacy Measure	
	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)
Duloxetine Delayed-Release Capsules 20 mg/day[a]	21.5 (4.10)	-10.9 (0.70)
Duloxetine Delayed-Release Capsules 60 mg/day[a]	21.1 (3.71)	-6.1 (0.69)
Fluoxetine 20 mg/day	20.3 (3.32)	-10.5 (0.71)
Placebo	20.3 (3.42)	-8.3 (0.67)

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval; not groups were included.

[a] Statistically significantly superior to placebo.

Study MDD-5 was a 6-week placebo-controlled study in adult patients with major depressive disorder and severe pain. Patients were randomized to duloxetine delayed-release capsules 60 mg or 120 mg once daily or to placebo. The primary efficacy variable was the change from baseline to the last visit on the 17-item Hamilton Depression Rating Scale (HAMD-17) total score. The figure and corresponding table below display the results for the primary efficacy variable and the HAMD-17 total score for this study.

Figure 1: Cumulative Proportion of Patients with Nausea

Table 7: Summary of the Primary Efficacy Results for Adult Trials in MDD Patients with Severe Pain

Treatment Group	Primary Efficacy Measure	
	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)
Duloxetine Delayed-Release Capsules 60 mg/day[a]	21.5 (4.10)	-10.9 (0.70)
Duloxetine Delayed-Release Capsules 120 mg/day[a]	21.1 (3.71)	-6.1 (0.69)
Placebo	20.3 (3.32)	-10.5 (0.71)
Duloxetine Delayed-Release Capsules 20 mg/day[a]	20.3 (3.42)	-8.3 (0.67)
Placebo	19.8 (3.58)	-2.4 (-4.7, -0.2)

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval; not groups were included.

[a] Statistically significantly superior to placebo.

Figure 2: Percentage of Patients with Severe Pain

Figure 3: Cumulative Proportion of Patients with Nausea

Figure 4: Percentage of Patients with Severe Pain

Figure 5: Percentage of Adult Patients with GAD Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study GAD-1)

Figure 6: Percentage of Adult Patients with GAD Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study GAD-2)

Figure 7: Percentage of Adult Patients with GP Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study CLEP-3)

Figure 8: Percentage of Adult Patients with CLBP Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study CLBP-3)

Figure 9: Percentage of Adult Patients with OA Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study OA-1)

Figure 10: Percentage of Adult Patients with OA Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study OA-2)

Figure 11: Percentage of Adult Patients with OA Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study OA-3)

Figure 12: Percentage of Adult Patients with OA Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study OA-4)

Figure 13: Percentage of Adult Patients with CLBP Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study CLBP-4)

Figure 14: Percentage of Adult Patients with CIPN Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study CIPN-1)

Figure 15: Percentage of Adult Patients with OP Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study CLEP-2)

Figure 16: Percentage of Adult Patients with SUI Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study SUI-1)

Figure 17: Percentage of Adult Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study UI-1)

Figure 18: Percentage of Adult Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study UI-2)

Figure 19: Percentage of Adult Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study UI-3)

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

Table 8: Summary of the Primary Efficacy Results for Adult Trials in MDD

Study Number	Treatment Group	Primary Efficacy Measure: HAMD-17	
		Mean Baseline Score (SD)	Placebo-adjusted Mean Change from Baseline (95% CI)
Study MDD-1	Duloxetine Delayed-Release Capsules 60 mg/day[a]	21.5 (4.10)	-10.9 (0.70)
	Duloxetine Delayed-Release Capsules 120 mg/day[a]	21.1 (3.71)	-6.1 (0.69)
	Placebo	21.3 (3.82)	–
Study MDD-2	Duloxetine Delayed-Release Capsules 60 mg/day[a]	20.3 (3.32)	-10.5 (0.71)
	Duloxetine Delayed-Release Capsules 120 mg/day[a]	20.3 (3.42)	-8.3 (0.67)
	Placebo	19.8 (3.58)	-2.4 (-4.7, -0.2)
Study MDD-3	Duloxetine Delayed-Release Capsules 20 mg/day[a]	17.2 (5.11)	-5.0 (0.81)
	Duloxetine Delayed-Release Capsules 60 mg/day[a]	18.1 (4.52)	-3.6 (-5.9, -1.4)
	Placebo	19.9 (3.54)	-11.0 (0.49)
Study MDD-4	Duloxetine Delayed-Release Capsules 60 mg/day[a]	20.2 (3.41)	-12.1 (0.49)
	Duloxetine Delayed-Release Capsules 120 mg/day[a]	19.9 (3.58)	-8.8 (0.50)
	Placebo	20.1 (3.58)	-8.8 (0.50)

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval; not groups were included.

[a] Statistically significantly superior to placebo.

Figure 20: Percentage of Adult Patients with GP Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study CLEP-3)

Figure 21: Percentage of Adult Patients with CLBP Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study CLBP-3)

Figure 22: Percentage of Adult Patients with OA Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study OA-1)

Figure 23: Percentage of Adult Patients with OA Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study OA-2)

Figure 24: Percentage of Adult Patients with OA Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study OA-3)

Figure 25: Percentage of Adult Patients with OA Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study OA-4)

Figure 26: Percentage of Adult Patients with CLBP Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study CLBP-4)

Figure 27: Percentage of Adult Patients with CIPN Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study CIPN-1)

Figure 28: Percentage of Adult Patients with OP Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study CLEP-2)

Figure 29: Percentage of Adult Patients with SUI Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study SUI-1)

Figure 30: Percentage of Adult Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study UI-1)

Figure 31: Percentage of Adult Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study UI-2)

Figure 32: Percentage of Adult Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study UI-3)

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Duloxetine Delayed-Release Capsules USP, 20 mg are Opaque green cap/Opaque green body size '4' hard gelatin capsule imprinted with 'H' on cap and '192' on body, filled with white to off white colored pellets.

Bottles of 30 Capsules	(NDC-31722-169-30)
Bottles of 60 Capsules	(NDC-31722-169-60)
Bottles of 90 Capsules	(NDC-31722-169-90)
Bottles of 1000 Capsules	(NDC-31722-169-10)
Blister Card of 7 Unit-Dose Capsules	(NDC-31722-169-31)
Blister Pack of 98 (7x14) Unit-Dose Capsules	(NDC-31722-169-52)

Duloxetine Delayed-Release Capsules USP, 30 mg are Opaque blue cap/Opaque white body size '3' hard gelatin capsule imprinted with 'H' on cap and '193' on body, filled with white to off white colored pellets.

Bottles of 30 Capsules	(NDC-31722-169-30)
Bottles of 60 Capsules	(NDC-31722-169-60)
Bottles of 90 Capsules	(NDC-31722-169-90)
Bottles of 1000 Capsules	(NDC-31722-169-10)
Blister Card of 7 Unit-Dose Capsules	(NDC-31722-169-31)
Blister Pack of 98 (7x14) Unit-Dose Capsules	(NDC-31722-169-52)

Duloxetine Delayed-Release Capsules USP, 60 mg are Opaque green cap/Opaque green body size '1' hard gelatin capsule imprinted with 'H' on cap and '195' on body, filled with white to off white colored pellets.

Bottles of 30 Capsules	(NDC-31722-170-30)
Bottles of 60 Capsules	(NDC-31722-170-60)
Bottles of 90 Capsules	(NDC-31722-170-90)
Bottles of 1000 Capsules	(NDC-31722-170-10)
Blister Card of 7 Unit-Dose Capsules	(NDC-31722-170-31)
Blister Pack of 98 (7x14) Unit-Dose Capsules	(NDC-31722-170-52)

16.2 Storage and Handling

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Suicidal Thoughts and Behaviors - Advise patients, their families, and their caregivers to observe for suicidal thoughts and behaviors, especially during initial treatment or when any dose is adjusted up or down and report these symptoms to their healthcare provider (*see Boxed Warning and Warnings and Precautions (5.1)*).

Hepatotoxicity - Inform patients that severe liver problems, sometimes fatal, have been associated with duloxetine delayed-release capsules treatment. Advise patients to promptly talk to their healthcare provider if they develop aching, right upper belly pain, dark urine, yellowish skin or eyes, nausea, vomiting, or unexplained flu-like symptoms lasting more than a few days (*see Warnings and Precautions (5.2)*).

Mydriasis - Advise patients that duloxetine delayed-release capsules may cause mydriasis (pupil dilation) which may in susceptible individuals, lead to acute angle closure glaucoma (*see Warnings and Precautions (5.3)*).

Orthostatic Hypotension, Falls and Syncope - Advise