Concomitant use of an MAOI antidepressant with duloxetine delayed-release capsules are contraindicated Use of duloxetine delayed-release capsules within 14 days of stopping an MAOI antidepressant is contraindicated

 $\underline{\textbf{Orthostatic Hypotension, Falls and Syncope:}} \textbf{Consider dosage reduction or discontinuation if these events occur (5.3)}$

of blisters, peeling rash, mucosal erosions, or any other sign of hypersensitivity if no other etiology can be identified (5.6)

Blood Pressure Increases: Monitor blood pressure prior to initiating treatment and periodically throughout treatment (5.11)

lucose Control in Diabetes: In DPNP patients, increases in fasting blood glucose, and HbA_{1c} have been observed (5.14)

hibbitors of PyP1A2 or Thioridazine: Avoid co-administration with duloxetine delayed-release capsules (5.12) Hyponatremia: Can occur in association with SIADH; consider discontinuation (5.13)

Sexual Dysfunction: Duloxetine delayed-release capsules may cause symptoms of sexual dysfunction (5.16)

Angle-Closure Glaucoma: Has occurred in patients with untreated anatomically narrow angles treated with antidepressants (5.9)

use or evidence of chronic liver disease (5.2)

release capsules and serotonergic agents (5.4)

Potent inhibitors of CYP1A2 should be avoided (7.1)

Duloxetine is a moderate inhibitor of CYP2D6 (7.9)

irritability) in the neonate (8.1)

Seizures: Prescribe with care in patients with a history of seizure disorder (5.10)

Conditions that Slow Gastric Emptying: Use cautiously in these patients (5.14)

<u>Adults</u>: nausea, dry mouth, somnolence, constipation, decreased appetite, and hyperhidrosis <u>Pediatric Patients</u>: decreased weight, decreased appetite, nausea, vomiting, fatigue, and diarrhea

Hepatic Impairment: Avoid use in patients with chronic liver disease or cirrhosis (5.14)

 $\underline{\textit{Renal Impairment:}} \ \textit{Avoid use in patients with severe renal impairment, GFR} < 30 \ \text{mL/minute} \ (5.14)$

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

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

In line rollid-or intravenous methylene blue-treated natients, initiation of duloxetine delayed-release cansules are contraindicated (4)

····CONTRAINDICATIONS····

......WARNINGS AND PRECAUTIONS

Hepatotoxicity: Hepatic failure, sometimes fatal, has been reported. Discontinue duloxetine delayed-release capsules in patients who develop jaundice or other

evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established. Avoid use in patients with substantial alcohol

Serotonin Syndrome: Increased risk when co-administered with other serotonergic agents, but also when taken alone. If it occurs, discontinue duloxetine delayed-

Increased Risk of Bleeding: May increase the risk of bleeding events. Concomitant use of antiplatelet drugs and anticoagulants may increase this risk (5.5, 7.4, 8.1)

Severe Skin Reactions: Severe skin reactions, including erythema multiforme and Stevens-Johnson Syndrome (SJS), can occur; Discontinue at the first appearance

Activation of Mania or Hypomania: Prior to initiating, screen patients for personal or family history of bipolar disorder, mania, or hypomania (5.8)

.....ADVERSE REACTIONS ..

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

....DRUG INTERACTIONS

....USE IN SPECIFIC POPULATIONS.....

Pregnancy: Third trimester use may increase risk for symptoms of poor adaptation (respiratory distress, temperature instability, feeding difficulty, hypotonia, tremor,

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 tion for DULOXETINE DELAYED-RELEASE CAPSULES. DULOXETINE delayed-release capsules, for oral use

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS See full prescribing information for complete boxed warning. ased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepre Monitor for worsening and emergence of suicidal thoughts and behaviors (5.1) -- RECENT MAJOR CHANGES --Warnings and Precautions (5.4, 5.5)

--INDICATIONS AND USAGE -Duloxetine delayed-release capsules are a serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for the treatment of the following conditions: Major depressive disorder (MDD) in adults (1) Generalized anxiety disorder (GAD) in adults and pediatric patients 7 years of age and older (1)

Diabetic peripheral neuropathic pain (DPNP) in adults (1) Fibromyalgia (FM) in adults and pediatric patients 13 years of age and older (1) Chronic musculoskeletal pain in adults (1)

...DOSAGE AND ADMINISTRATION ... Take duloxetine delayed-release capsules once daily, with or without food. Swallow whole; do not crush, chew, or open capsule (2.1) Starting Dose

		I .	
MDD (2.2)	40 mg/day to 60 mg/day	Acute Treatment: 40 mg/day (20 mg twice daily) to 60 mg/day (once daily or as 30 mg twice daily); Maintenance Treatment: 60 mg/day	120 mg/day
GAD (2.3) Adults Geriatric Pediatrics (7 to 17 years of age)	60 mg/day 30 mg/day 30 mg/day	60 mg/day (once daily) 60 mg/day (once daily) 30 to 60 mg/day (once daily)	120 mg/day 120 mg/day 120 mg/day
DPNP (2.4)	60 mg/day	60 mg/day (once daily)	60 mg/day
FM (2.5) Adults and Pediatrics (13 to 17 years of age)	30 mg/day	60 mg/day (once daily)	60 mg/day
Chronic Musculoskeletal Pain (2.6)	30 mg/day	60 mg/day (once daily)	60 mg/day

Discontinuing duloxetine delayed-release capsules: Gradually reduce dosage to avoid discontinuation symptoms (2.8, 5.7) ····DOSAGE FORMS AND STRENGTHS--

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

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Initial U.S. Approval: 2004

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 Dosage for Treatment of Generalized Anxiety Disorder
- 2.4 Dosage for Treatment of Diabetic Peripheral Neuropathic Pain in Adults Dosage for Treatment of Fibromyalgia
 Dosage for Treatment of Chronic Musculoskeletal Pain in Adults Dosage in Patients with Hepatic Impairment or Severe Renal Impairment
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FULL PRESCRIBING INFORMATION

(5.1)].

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS idepressants 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

1 INDICATIONS AND USAGE Duloxetine delayed-release capsules are indicated for the treatment of: Major depressive disorder in adults

- Generalized anxiety disorder in adults and pediatric patients 7 years of age and older
- Diabetic peripheral neuropathic pain in adults Fibromyalgia in adults and pediatric patients 13 years of age and older
- Chronic musculoskeletal pain in adul 2 DOSAGE AND ADMINISTRATION

and Administration (2.7) and Use in Specific Populations (8.10)).

2.1 Important Administration Instructions Administer duloxetine delayed-release capsules orally (with or without meals) and swallow whole. Do not chew or crush, and do not open the delayed-release capsule an

sprinkle its contents on food or mix with liquids because these actions might affect the enteric coating. If a dose of duloxetine delayed-release capsules is missed, take the nissed dose as soon as it is remembered. If it is almost time for the next dose, skip the missed dose and take the next dose at the regular time. Do not take two doses of e delayed-release capsules at the same time 2.2 Dosage for Treatment of Major Depressive Disorder in Adults The recommended starting dosage in adults with MDD is 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 duloxetine delayed-release capsules 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. Periodically reassess to determine the need for maintenance treatment and the appropriate dosage for such treatment 2.3 Dosage for Treatment of Generalized Anxiety Disorder Recommended Dosage in Adults Less than 65 Years of Age
For most adults less than 65 years of age with GAD, initiate duloxetine delayed-release capsules 60 mg once daily. For some patients, it may be desirable to start at 30 mg

once daily for 1 week, to allow patients to adjust to duloxetine delayed-release capsules before increasing to 60 mg once daily. While a 120 mg once daily dosage 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 dosage beyond 60 mg once daily, increase dosage in increments of 30 mg once daily. Periodically reassess to determine the continued need for maintenance treatment and the appropriate dosage for such treatment. Recommended Dosage in Geriatric Patients

In geriatric patients with GAD, initiate duloxetine delayed-release capsules at a dosage of 30 mg once daily for 2 weeks before considering an increase to the target dose of 60 mg/day. Thereafter, patients may benefit from doses above 60 mg once daily. If a decision is made to increase the dose beyond 60 mg once daily, increase dose in increments of 30 mg once daily. The maximum dose studied was 120 mg per day Recommended Dosage in Pediatric Patients 7 to 17 Years of Age Initiate duloxetine delayed-release capsules in pediatric patients 7 to 17 years of age with GAD at a dosage of 30 mg once daily for 2 weeks before considering an increas

to 60 mg once daily. The recommended dosage range is 30 to 60 mg once daily. Some patients may benefit from dosages above 60 mg once daily. If a decision is made to increase the dose beyond 60 mg once daily, increase dosage in increments of 30 mg once daily. The maximum dose studied was 120 mg per day. 2.4 Dosage for Treatment of Diabetic Peripheral Neuropathic Pain in Adults Administer 60 mg once daily in adults with diabetic peripheral neuropathic pain. There is no evidence that doses higher than 60 mg once daily confer additional significant benefit and the higher dosage is clearly less well tolerated. For patients for whom tolerability is a concern, a lower starting dose may be considere Since diabetes is frequently complicated by renal disease, consider a lower starting dosage and gradual increase in dosage for patients with renal impairment (see Dosage

2.5 Dosage for Treatment of Fibromyalgia Recommended Dosage in Adults The recommended duloxetine delayed-release capsules dosage is 60 mg once daily in adults with fibromyalgia. Begin treatment at 30 mg once daily for 1 week, to allow patients to adjust to duloxetine delayed-release capsules before increasing to 60 mg once daily. Some patients may respond to the starting dosage. There is no evidence that dosages greater than 60 mg/day confer additional benefit, even in patients who do not respond to a 60 mg/day dosage, and higher dosages were associated with a

 $\underline{Recommended\ Dosage\ in\ Pediatric\ Patients\ 13\ to\ 17\ Years\ of\ Age}$ The recommended starting duloxetine delayed-release capsules dosage in pediatric patients 13 to 17 years of age with fibromyalgia is 30 mg once daily. The dosage may be increased to 60 mg once daily based on response and tolerability. 2.6 Dosage for Treatment of Chronic Musculoskeletal Pain in Adults

The recommended duloxetine delayed-release capsules dosage is 60 mg once daily in adults with chronic musculoskeletal pain. Begin treatment at 30 mg once daily for one week, to allow patients to adjust to duloxetine delayed-release capsules before increasing to 60 mg once daily. There is no evidence that higher dosages confer additional benefit, even in patients who do not respond to a 60 mg once daily dosage, and higher dosages are associated with a higher rate of adverse reactions /see Clinical Studies

2.7 Dosage in Patients with Hepatic Impairment or Severe Renal Impairment

Avoid use in patients with chronic liver disease or cirrhosis *(see Warnings and Precautions (5.14) and Use in Specific Populations (8.9)*]. Avoid use in patients with severe renal impairment, GFR < 30 mL/minute/see Warnings and Precautions (5.14) and Use in Specific Populations (8.10)/

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

2.9 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

2.10 Use of Duloxetine Delayed-Release Capsules with Other MAOIs such as Linezolid or Methylene Blue Do not start duloxetine delayed-release capsules in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered /see Contraindications (4)].

In some cases, a patient already receiving duloxetine delayed-release capsules therapy may require urgent treatment with linezolid or intravenous methylene blue. If an acceptable alternatives to linearity recovering during the content of the content are not available and the potential benefits of intravenous methylene blue treatment are not available and the potential benefits of intravenous methylene blue treatment are pudged 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 natient 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

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20 mg are Opaque green cap/Opaque green body size '4' hard gelatin capsule imprinted with 'H' on cap and '190' on body, filled with white to off white colored pellets. 30 mg are Opaque blue cap/Opaque white body size '3' hard gelatin capsule imprinted with 'H' on cap and '191' on body, filled with white to off white colored pellets. 60 mg Opaque blue cap/ Opaque green body size '1' hard gelatin capsule imprinted with 'H' on cap and '192' on body, filled with white to off white colored pellets. 4 CONTRAINDICATIONS The use of MAOIs intended to treat psychiatric disorders with duloxetine delayed-release capsules or within 5 days of stopping treatment with duloxetine delayed-releas

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 contraindicated (see Dosage and Administration (2.8) and Warnings and Precautions (5.4)] Starting duloxetine delayed-release capsules in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because eased risk of serotonin syndrome/see Dosage and Administration (2.9) and Warnings and Precautions (5.4)].

5.1 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission

occurs. Suicide is a known risk of degression 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 patien during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies

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 ndications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in 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
mber was not sufficient to reach any con	duloxetine delayed-release capsules trials. There were suicides in the adult duloxetine delayed-release capsules trials, but th clusion about duloxetine delayed-release capsules effect on suicide. extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlle

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. ing symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomani and mania, have been reported in adult and pediatric patients being treated with antidepressants for maior 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. ideration 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.

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triptans used to treat n medicines used to tre including tricyclics, lith tramadol, fentanyl, meg amphetamines

about esses,

What is the most important information I should antidepressant medicines, depression, other serious menand suicidal thoughts or actions?

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 (2.8) 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.

There have been reports of benatic failure, sometimes fatal, in patients treated with duloxetine delayed release capsules. These cases have presented as benatitis with abdominal pain, hepatomegaly, and elevation of transaminase levels to more than twenty times the upper limit of normal (ULN) with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Duloxetine delayed-release capsules should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported. Other postmarketing reports indicate that elevated transaminases, bilirubin, and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis Duloyeting delayed-release cansules increased the risk of elevation of serum transaminase levels in development program clinical trials. Liver transaminase elevation

esulted in the discontinuation of 0.3% (92/34,756) of duloxetine delayed-release capsules-treated patients. In most patients, the median time to detection of the nase elevation was about two months. In adult placebo-controlled trials, for patients with normal and abnormal baseline ALT values, elevation of ALT > 3 times the ULN occurred in 1.25% (144/11,496) of duloxetine delayed-release capsules-treated patients compared to 0.45% (39/8716) of placebo-treated patients. In adult placebo-controlled studies using a fixed dose design, there was evidence of a duloxetine delayed-release capsules dose response relationship for ALT and AST elevation of > 3 times the ULN and > 5 times the ULN, respectively. Because it is possible that duloxetine delayed-release capsules and alcohol may interact to cause liver injury or that duloxetine delayed-release capsules may aggravate pre-existing liver disease, duloxetine delayed-release capsules should not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease Orthostatic Hypotension, Falls and Syncope

Orthostatic hypotension, falls, and syncope have been reported in patients treated with the recommended duloxetine delayed-release capsules dosages. Syncope and orthostatic hypotension tend to occur within the first week of therapy but can occur at any time during duloxetine delayed-release capsules treatment, particularly after dose increases. The risk of falling appears to be related to the degree of orthostatic decrease in blood pressure (BP) as well as other factors that may increase the underlying risk of falls. In an analysis of patients from all placebo-controlled trials, patients treated with duloxetine delayed-release capsules reported a higher rate of falls compared to patients treated with placebo. Risk appears to be related to the presence of orthostatic decrease in BP. The risk of BP decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as antihypertensives) or are potent CYP1A2 inhibitors (see Warnings and Precautions (5.12) and Drug Interaction

(7.1)] and in patients taking duloxetine delayed-release capsules at doses above 60 mg daily. Consideration should be given to dose reduction or discontinuation of capsules in patients who experience symptomatic orthostatic hypotension, falls and/or syn Risk of falling also appeared to be proportional to a patient's underlying risk for falls and appeared to increase steadily with age. As geriatric patients tend to have a higher underlying risk for falls due to a higher prevalence of risk factors such as use of multiple medications, medical comorbidities and gait disturbances, the impact of increasing age by itself is unclear. Falls with serious consequences including fractures and hospitalizations have been reported with duloxetine delayed-release capsules use [se

5.4 Serotonin Syndrome repinephrine reuptake inhibitors (SNRIs), including duloxetine delayed-release capsules, can precipitate serotonin syndrome, a potentially life-threatening condition. The risk is increased with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, meperidii methadone, tryptophan, buspirone, amphetamines, and St. John's Wort) and with drugs that impair metabolism of serotonin, i.e., MAOIs, (see Contraindications (4), Drug teractions (7.13)]. Serotonin syndrome can also occur when these drugs are used alone. tonin syndrome signs and symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia,

labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The concomitant use of duloxetine delayed-release capsules with MAOIs is contraindicated. In addition, do not initiate duloxetine delayed-release capsules in a patient being treated with MAOIs such as linezolid or intravenous methylene blue. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection). If it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking duloxetine delayed-release capsules, discontinue duloxetine delayed-release capsules before initiating treatment with the MAOI (see Contraindications (4) and Drug Interactions (7.13)). Monitor all patients taking duloxetine delayed-release capsules for the emergence of serotonin syndrome. Discontinue treatment with duloxetine delayed-release capsules and any concomitant serotonergic agents immediately if the above symptoms occur, and initiate supportive symptomatic treatment. If concomitant user of duloxetine delayed-release capsules with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome and monitor for symptoms. 5.5 Increased Risk of Bleeding

Drugs that interfere with serotonin reuptake inhibition, including duloxetine delayed-release capsules, may increase the risk of bleeding events. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. A post-marketing study showed a higher incidence of postpartum hemorrhage in mothers taking duloxetine delayed-release capsules. Other bleeding events related to SSRI and SNRI use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anti-coagulants may add to this risk. Inform patients about the risk of increased bleeding associated with the concomitant use of duloxetine delayed-release capsules and NSAIDs, aspirin, or other drugs that affect coagulation [see Drug Interactions (7.4)]. 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 Syndrome placebo-controlled clinical trials, the following symptoms occurred at 1% or greater and at a significantly higher rate in duloxetine delayed-release capsules-treated atients compared to those discontinuing from placebo: dizziness, headache, nausea, diarrhea, paresthesia, irritability, vomiting, insomnia, anxiety, hyperhidrosis, and During marketing of other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon tinuation 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 healthcare provider may continue decreasing the dose but at a more gradual rate (see Dosage and

5.8 Activation of Mania/Hypomania In adult placebo-controlled trials in patients with MDD, activation of mania or hypomania was reported in 0.1% (4/3779) of duloxetine delayed-release capsules-treated patients and 0.04% (1/2536) of placebo-treated patients. No activation of mania or hypomania was reported in DPNP, GAD, fibromyalgia, or chronic musculoskeletal pain placebo-controlled trials. Activation of mania or hypomania has been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs effective in the treatment of major depressive disorder. As with these other agents, duloxetine delayed-release capsules should be used cautiously in patien

The pupillary dilation that occurs following use of many antidepressant drugs including duloxetine delayed-release capsules may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy. 5.10 Seizures Duloxetine delayed-release capsules has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. In adult placebo-controlled clinical trials, seizures/convulsions occurred in 0.02% (3/12,722) of patients treated with duloxetine delayed-release capsules and 0.01% (1/9513) of nationts treated with placeho. Duloxetine delayed-release cansules should be prescribed with care in nationts with a history of a seizure disorder

In adult placebo-controlled clinical trials across the approved adult populations from baseline to endpoint, duloxetine delayed-release capsules treatment was associated with mean increases of 0.5 mm Hg in systolic blood pressure and 0.8 mm Hg in 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 delayed-release capsules 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 (approximately 3.3 times the max recommended dosage). 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. e should be measured prior to initiating treatment and periodically 5.12 Clinically Important Drug Interactions Both CYP1A2 and CYP2D6 are responsible for duloxetine delayed-release capsules 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)].

5.9 Angle-Closure Glaucoma

CYP2D6 Inhibitors - Because CYP2D6 is involved in duloxetine delayed-release capsules metabolism, concomitant use of duloxetine delayed-release capsules with pote inhibitors of CYP2D6 would be expected to, and does, result in higher concentrations (on average of 60%) of duloxetine delayed-release capsules [see Drug Interactions 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]]. delayer-leases capacies strough for the prescribed in patients with a usuasimular action users evaluating and recognizing strategies of the primary CNS effects of duloxetine delayed-release capacities, it should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action/see Warnings and Precautions (5.12) and Drug Interactions (7.16)/.

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including duloxetine delayed-release capsules. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported with duloxetine delayed-release capsules use and appeared to be reversible when duloxetine delayed-release capsules were discontinued. Geriatric patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk /see Use in Specific Populations (8.5)). Discontinuation of duloxetine delayed-release capsules should be considered in patients with symptomatic hyponatremia and appropriate medical

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

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

Hepatic Impairment Avoid use in patients with chronic liver disease or cirrhosis [see Dosage and Administration (2.7), Warnings and Precautions (5.2), and Use in Specific Populations (8.9)]. Severe Renal Impairment

Avoid use in patients with severe renal impairment, GFR < 30 mL/minute. Increased plasma concentration of duloxetine delayed-release capsules, and especially of its metabolites, occurred in patients with end-stage renal disease (requiring dialysis) [see Dosage and Administration (2.7) and Use in Specific Populations (8.10)]. Glycemic Control in Patients with Diabetes As observed in DPNP trials, duloxetine delayed-release capsules treatment worsened 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 (see Clinical Studies (14.4)), the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 176 mg/dL, and the mean baseline hemoglobin A1 c (HbA1c) was 7.8%. In the 12-week acute treatment phase of these studies, duloxetine delayed-release capsules were associated with a small increase in mean fasting blood glucose as compared to placebo.

In the extension phase of these studies, which lasted up to 52 weeks, mean fasting blood plucose increased by 12 mg/dL in the duloxetine delayed-release capsules group ınd decreased by 11.5 mg/dL in the routine care group. HbA1c increased by 0.5% in the duloxetine delayed-release capsules group and by 0.2% in the routine care group. Duloxetine delayed-release capsules are in a class of drups 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 delayed-release capsules

5.16 Sexual Dysfunction Use of SNRIs, including duloxetine delayed-release capsules, may cause symptoms of sexual dysfunction (see Adverse Reactions (6.1)). In male patients, SNRI use may result in ejaculatory delay or failure, decreased libido, and erectile dysfunction. In female patients, SNRI use may result in decreased libido and delayed or absent orgas It is important for prescribers to inquire about sexual function prior to initiation of duloxetine delayed-release capsules and to inquire specifically about changes in sexual function during treatment, because sexual function may not be spontaneously reported. When evaluating changes in sexual function, obtaining a detailed history (including timing of symptom onset) is important because sexual symptoms may have other causes, including the underlying psychiatric disorder. Discuss potential management strategies to support patients in making informed decisions about treatment.

6 ADVERSE REACTIONS following serious adverse reactions are described below and elsewhere in the labeling:
Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults (see Boxed Warning and Warnings and Precautions (5.1)) Hepatotoxicity [see Warnings and Precautions (5.2)]

Orthostatic Hypotension, Falls and Syncope [see Warnings and Precautions (5.3)] Serotonin Syndrome (see Warnings and Precautions (5.4)) Severe Skin Reactions [see Warnings and Precautions (5.6)]

Discontinuation Syndrome [see Warnings and Precautions (5.7)]

Activation of Mania/Hypomania [see Warnings and Precautions (5.8)] Revised: 06/2024 Angle-Closure Glaucoma (see Warnings and Precautions (5.9))

Seizures (see Warnings and Precautions (5.10)) Increases in Blood Pressure [see Warnings and Precautions (5.11)] Clinically Important Drug Interactions (see Warnings and Precautions (5.12))

Hyponatremia (see Warnings and Precautions (5.13)) Urinary Hesitation and Retention [see Warnings and Precautions (5.15)] Sexual Dysfunction/see Warnings and Precautions (5.16)/ 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The stated frequencies of adverse reactions represent the proportion of patients who experienced, at least once, one treatment-emergent adverse reaction of the type listed. A reaction was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. Adverse Reactions in Adults

The data described below reflect exposure to duloxetine delayed-release capsules in placebo-controlled adult trials for MDD (N=3779), GAD (N=1018), OA (N=503), CLBP (N – 600), DPNP (N – 906), and FM (N – 1294). The age range in this pooled population was 17 to 89 years of age. In this pooled population, 66%, 61%, 43%, and 94% of adult patients were female; and 82%, 73%, 85%, 74%, and 86% of adult patients were Caucasian in the MDD, GAD, OA and CLBP, DPNP, and FM populations, respectively. Most patients received duloxetine delayed-release capsules dosages of a total of 60 to 120 mg per day [see Clinical Studies (14]]. The data below do not include results of the trial that evaluated the efficacy of duloxetine delayed-release capsules for the treatment of GAD in patients \geq 65 years old (Study GAD-5) /see Clinical Studies (14.3)/; however, the adverse reactions observed in this geriatric population were generally similar to adverse reactions in the overall adult population.

 $\underline{\textbf{Adverse Reactions Leading to Treatment Discontinuation in Adult Placebo\cdot Controlled Trials}$ Major Depressive Disorder imately 8.4% (319/3779) of duloxetine delayed-release capsules-treated patients in placebo-controlled adult trials for MDD discontinued treatment due to an adverse reaction, compared with 4.6% (117/2536) of placebo-treated patients. Nausea (duloxetine delayed-release capsules 1.1%, placebo 0.4%) was the only adverse reaction reported as a reason for discontinuation and considered to be drug- related (i.e., discontinuation occurring in at least 1% of the duloxetine delayed-release

capsules-treated patients and at a rate of at least twice that of placebo-treated patients). Generalized Anxiety Disorder Approximately 13.7% (139/1018) of the duloxetine delayed-release capsules-treated patients in placebo-controlled adult trials for GAD discontinued treatment due to an adverse reaction, compared with 5% (38/767) for placebo-treated patients. Common adverse reactions reported as a reason for discontinuation and considered to be drug-

elated (as defined above) included nausea (duloxetine delayed-release capsules 3.3%, placebo 0.4%), and dizziness (duloxetine delayed-release capsules 1.3%, placebo Approximately 12.9% (117/906) of the duloxetine delayed-release capsules-treated natients in placeho-controlled adult trials for DPNP discontinued treatment due to an

Application, compared with 5.1% (23/448) for placebo-treated patients. Common adverse reactions, reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine delayed-release capsules 3.5%, placebo 0.7%), dizziness (duloxetine delayed-release capsules 1.2%, placebo 0.4%), and somnolence (duloxetine delayed-release capsules 1.1%, placebo 0%). Fibromyalgia

Approximately 17.5% (227/1294) of the duloxetine delayed-release capsules-treated patients in 3- to 6-month placebo-controlled adult trials for FM discontinued treatment due to an adverse reaction, compared with 10.1% (96/955) for placebo-treated patients. Adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine delayed-release capsules 2.0%, placebo 0.5%), headache (duloxetine delayed-releas apsules 1.2%, placebo 0.3%), somnolence (duloxetine delayed-release capsules 1.1%, placebo 0%), and fatigue (duloxetine delayed-release capsules 1.1%, placebo Approximately 15.7% (79/503) of the duloxetine delayed-release capsules-treated patients in 13-week, placebo-controlled adult trials for chronic pain due to OA

and considered to be drug-related (as defined above) included nausea (duloxetine delayed-release capsules 2.2%, placebo 1%). Chronic Low Back Pair Approximately 16.5% (99/600) of the duloxetine delayed-release capsules-treated natients in 13-week, placeho-controlled adult trials for CLBP discontinued treatment due to an adverse reaction, compared with 6.3% (28)4411 for placebo-treated patients. Adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine delayed-release capsules 3%, placebo 0.7%), and somnolence (duloxetine delayed-release capsules 1%,

Most Common Adverse Reactions in Adult Trials

he most commonly observed adverse reactions in duloxetine delayed-release cansules-treated natients (as defined aboye) were: Diabetic Peripheral Neuropathic Pain: nausea, somnolence, decreased appetite, constipation, hyperhidrosis, and dry mouth. Fibromyalgia: nausea, dry mouth, constination, somnolence, decreased annetite, hyperhidrosis, and agitation, Chronic Pain due to Osteoarthritis: nausea, fatigue, constipation, dry mouth, insomnia, somno

Chronic Low Back Pain: nausea, dry mouth, insomnia, somnolence, constipation, dizziness, and fatigue. mmonly observed adverse reactions in duloxetine delayed-release capsules-treated patients in all the pooled adult populations (i.e., MDD, GAD, DPNP, FM, OA, and CLBP) (incidence of at least 5% and at least twice the incidence in placebo-treated patients) were nausea, dry mouth, somnolence, constipation, decreased appetite,

Table 2 displays the incidence of adverse reactions in placeho-controlled trials for approved adult populations (i.e. MDD, GAD, DPNP, EM, OA, and CLRP) that occurred in $5\%\ or\ more\ of\ dulox etine\ delayed\ - release\ capsules\ - treated\ patients\ and\ with\ an\ incidence\ greater\ than\ placebo\ - treated\ patients\ and\ with\ an\ incidence\ greater\ than\ placebo\ - treated\ patients\ and\ with\ an\ incidence\ greater\ than\ placebo\ - treated\ patients\ and\ with\ an\ incidence\ greater\ than\ placebo\ - treated\ patients\ and\ with\ an\ incidence\ greater\ than\ placebo\ - treated\ patients\ and\ with\ an\ incidence\ greater\ than\ placebo\ - treated\ patients\ and\ placebo\ - treated\ patien$ Table 2: Adverse Posetions: Incidence of EW or More and Greater than Placeho in Placeho Controlled Trials of A

	Percentage of Patients Rep	Percentage of Patients Reporting Reaction			
Adverse Reaction	Duloxetine Delayed-Release Capsules (N=8100)	Placebo (N=5655)			
Nausea ^c	23	8			
Headache	14	12			
Dry mouth	13	5			
Somnolence ^e	10	3			
Fatigue ^{b,c}	9	5			
Insomnia ^d	9	5			
Constipation ^c	9	4			
Dizziness ^c	9	5			
Diarrhea	9	6			
Decreased appetite ^c	7	2			
Hyperhidrosis ^c	6	1			
Abdominal pain ^f	5	4			

Includes adults with MDD, GAD, DPNP, FM, and chronic musculoskeletal pain. 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 intege 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.

⁴Also includes initial insomnia, middle insomnia, and early morning awakening. 'Also includes hypersomnia and sedation.

'Also includes abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, and gastrointestinal pain Adverse Reactions in Pooled MDD and GAD Trials in Adults Table 3 displays the incidence of adverse reactions in MDD and GAD placebo-controlled adult trials that occurred in 2% or more of duloxetine delayed-release capsulestreated patients and with an incidence greater than placebo-tre

	Percentage of Patients Reporting Reaction			
System Organ Class / Adverse Reaction	Duloxetine Delayed-Release Capsules (N = 4797)	Placebo (N = 3303)		
Cardiac Disorders				
Palpitations	2	1		
Eye Disorders				
Vision blurred	3	1		
Gastrointestinal Disorders				
Nausea ^c	23	8		
Dry mouth	14	6		
Constipation ^c	9	4		
Diarrhea Diarrhea	9	6		
Abdominal pain ^d	5	4		
Vomiting	4	2		
General Disorders and Administration Site Conditions				
Fatigue ^e	9	5		
Metabolism and Nutrition Disorders				
Decreased appetite ^c	6	2		
Nervous System Disorders				
Headache	14	14		
Dizziness ^c	9	5		
Somnolence ^f	9	3		
Tremor	3	1		
Psychiatric Disorders				
Insomnia®	9	5		
Agitation ^h	4	2		
Anxiety	3	2		
Reproductive System and Breast Disorders				
Erectile dysfunction	4	1		
Ejaculation delayed ^c	2	i		
Libido decreased	3	i		
Orgasm abnormal ⁱ	2	<1		
Respiratory, Thoracic, and Mediastinal Disorders				
Yawning	2	<1		
	4	<u> </u>		

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 neares ^bFor GAD, there were no adverse reactions that were significantly different between treatments in adults ≥ 65 years that were also not significant in the adults < 65 Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies which did not have a placeho lead-in period or ¹Includes abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort, and gastrointestinal pain

° Includes asthenia. Includes hypersomnia and sedation. ⁹ Includes initial insomnia, middle insomnia, and early morning awakening. Includes feeling jittery, nervousness, restlessness, tension and psychomotor hyperactivity

Skin and Subcutaneous Tissue Disorders

Includes anorgasmia. Adverse Reactions in the DPNP, FM, OA, and CLBP Adult Trials Table 4 displays the incidence of adverse reactions that occurred in 2% or more of duloxetine delayed-release capsules-treated patients (determined prior to rounding) in the premarketing acute phase of DPNP, FM, OA, and CLBP placebo-controlled adult trials and with an incidence greater than placebo-treated patien

Table 4: Adverse Reactions: Incidence of 2% or More and Greater than Placebo in DPNP, FM, OA, and CLBP Placebo Controlled Trials

	Percentage of Patients Reporting Reaction				
System Organ Class / Adverse Reaction	Duloxetine Delayed-Release Capsules (N=3303)	Placebo (N = 2352)			
Gastrointestinal Disorders					
Nausea	23	7			
Dry Mouth ^b	11	3			
Constipation ^b	10	3			
Diarrhea .	9	5			
Abdominal Pain ^c	5	4			
Vomiting	3	2			
Dyspepsia	2	1			
General Disorders and Administration					
Site Conditions					
Fatigue ^d	11	5			
nfections and Infestations					
Nasopharyngitis	4	4			
Upper Respiratory Tract Infection	3	3			
nfluenza	2	2			
Metabolism and Nutrition Disorders					
Decreased Appetite ^b	8	1			
Musculoskeletal and Connective Tissue					
Musculoskeletal Pain ^e	3	3			
Muscle Spasms	2	2			
Nervous System Disorders					
Headache	13	8			
Somnolence ^{b,f}	11	3			
Dizziness	9	5			
Paraesthesia®	2	2			
Tremor ^b	2	<1			
Psychiatric Disorders					
nsomnia ^{h,h}	10	5			
Agitation ⁱ	3	1			
Reproductive System and Breast Disorders					
Erectile Dysfunction ^b	4	<1			
Ejaculation Disorder	2	<1			
•	۷				
Respiratory, Thoracic, and Mediastinal Disorders Cough	2	2			
Skin and Subcutaneous Tissue Disorders Hyperhidrosis	6	1			
Vascular Disorders					
Flushing ^k	3	1			
Plood proceure incressed	J	l '			

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

a**nd falls.** Monitor y atment. Duloxetine

dark urine
 vellow skin or e,
 enlarged liver
 increased liver e
 changes in blood p
 starting and throug
 may:
 increase your ble

Includes abdominal discomfort, lower abdominal pain, upper abdominal pain, abdominal tenderness and gastrointestinal pain. How should I take duloxetine delayed-release capsules?
Take duloxetine.
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 foryou.
Swallow duloxetine delayed-release capsules whole. Do not chew or crush duloxetine delayed-release capsules whole. Do not pen the capsule may affect how well 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, take 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 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 concomitantly with heavy alcohol intake may be associated with severe liver injury. Avoid heavy alcohol use while taking duloxetine delayed-release capsules.
What are the possible side effects of duloxetine delayed-release capsules.

nt upper abdominal pain k urine

icine used to treat a rr (MDD). Duloxetine known as SNRIs (or

Incidence of 120 mg/day is significantly greater than the incidence for 60 mg/day.

What are the possible side effects capsules?
Duloxetine delayed-release capsules may ca See "What is the most important informatidelayed-release capsules?"
Common possible side effects in people whe capsules include:

1. Iiver damage. Symptoms may include

nber take . Do not ovider.

Includes asthenia Includes myalgia and neck pain.
Includes hypersomnia and sedation

Includes hypoaesthesia, facial hypoaesthesia, genital hypoaesthesia and oral paraesthesia.

Includes initial insomnia, middle insomnia, and early morning awakening.
Includes feeling jittery, nervousness, restlessness, tension and psychomotor hyperactivity Includes ejaculation failure.

Includes increased diastolic blood pressure, increased systolic blood pressure, diastolic hypertension, essential hypertension, hypertension, hypertension, hypertension, labile hypertension, orthostatic hypertension, secondary hypertension, and systolic hypertension Effects on Male and Female Sexual Function in Adults with MDD

Changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of psychiatric disorders or diabetes, but they may also be a consequence of pharmacologic treatment. Because adverse sexual reactions are presumed to be voluntarily underreported, the Arizona Sexual Experience Scale (ASEX), a validated measure designed to identify sexual adverse reactions, was used prospectively in 4 MDD placebo-controlled adult trials (Studies MDD-1, MDD-2, MDD-3, and MDD-4) [See Clinical Studies (14.2)]. The ASEX scale includes five questions that pertain to the following aspects of sexual function: 1) sex drive, 2) ease of arousal, 3) ability to achieve erection (men) or lubrication (women), 4) ease of reaching orgasm, and 5) orgasm satisfaction. Positive numbers signify a worsening of sexual function from baseline. Negative numbers signify an improvement from a baseline level of dysfunction, which is commonly seen in depressed patients. In these trials, duloxetine delayed-release capsules-treated male patients experienced significantly more sexual dysfunction, as measured by the total score on the ASEX

in these trials, universitied eclarge-inclusion spaces related intelligents experience significantly into exact organic prices of control that an experience with the control of the experience when the control of the experience when and the ability to reach organic, than placebo-treated male patients (see Table 5). Unlowerine delayed-release capsules-treated female patients did not experience more sexual dysfunction than placebo-treated female patients as measured by ASEX total score. Healthcare providers should routinely inquire about possible sexual adverse reactions in duloxetine delayed-release capsules-treated patients. Table 5: Mean Change in ASEX Scores by Gender in MDD Placeho Controlled Adult Triple

Table 5: Mean Change In ASEX Scores by Gender In MUD Placebo-Controlled Adult Trials					
	Male Patients		Female Patients ^a		
	Duloxetine Delayed-Release	Placebo	Duloxetine Delayed-	Placebo	
	Capsules	(n=83)	Release Capsules	(n=126)	
	(n=175)		(n=241)		
ASEX Total (Items 1-5)	0.56 ^b	-1.07	-1.15	-1.07	
Item 1 — Sex drive	-0.07	-0.12	-0.32	-0.24	
Item 2 — Arousal	0.01	-0.26	-0.21	-0.18	
Item 3 — Ability to achieve erection (men);	0.03	-0.25	-0.17	-0.18	
Lubrication (women)					
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	

an = Number of patients with non-missing change score for ASEX total. p=0.013 versus placebo

Laboratory Changes in Adults

quality sleep; Rare: dysarthria.

'p < 0.001 versus placebo Vital Sign Changes in Adults

In placebo-controlled clinical trials across approved adult populations for change from baseline to endpoint, Duloxetine delayed-release capsules-treated patients had mean increases of 0.23 mm Hg in systolic blood pressure (SBP) and 0.73 mm Hg in diastolic blood pressure (DBP) compared to mean decreases of 1.09 mm Hg in SBP and 0.55 mm Hn in DRP in placeho-treated nationts. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure (see Warning and Precautions (5.3, 5.11)]. Duloxetine delayed-release capsules treatment, for up to 26 weeks in placebo-controlled trials across approved adult populations, typically caused a small increase in heart rate for change from baseline to endpoint compared to placebo of up to 1.37 beats per minute (increase of 1.20 beats per minute in duloxetine delayed-release capsules-

sules treatment in placebo-controlled clinical trials across approved adult populations, was associated with small mean increases from baseline to endpoint in ALT, AST, CPK, and alkaline phosphatase; infrequent, modest, transient, abnormal values were observed for these analytes in duloxetine delayedrelease capsules-treated patients when compared with placebo-treated patients (see Warnings and Precautions (5.2)]. High bicarbonate, cholesterol, and abnormal (high or low) potassium, were observed more frequently in duloxetine delayed-release capsules-treated patients compared to placebo-treated patients. $\underline{Other\ Adverse\ Reactions\ Observed\ During\ the\ Clinical\ Trial\ Evaluation\ of\ Dulox etine\ Delayed\cdot Release\ Capsules\ in\ Adults}$ Following is a list of adverse reactions reported by patients treated with duloxetine delayed-release capsules in clinical adult trials. In clinical trials of all approved adult populations, 34,756 patients were treated with duloxetine delayed-release capsules. Of these, 27% (9337) took duloxetine delayed-release capsules for at least 6

months, and 12% (4317) took duloxetine delayed-release capsules for at least one year. The following listing is not intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) which occurred at a rate equal to or less than placebo. Reactions are categorized by body system according to the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients

Cardiac Disorders - Frequent: palpitations; Infrequent: myocardial infarction, tachycardia, and Takotsubo cardiomyopathy Ear and Labyrinth Disorders — Frequent: vertigo; Infrequent: ear pain and tinnitus.

treated patients, decrease of 0.17 beats per minute in placebo-treated patients)

Endocrine Disorders - Infrequent: hypothyroidism. <u>Eye Disorders</u> — *Frequent:* vision blurred; *Infrequent:* diplopia, dry eye, and visual impairment. Gastrointestinal Disorders — Frequent: flatulence; Infrequent: dysphagia, eructation, gastritis, gastrointestinal hemorrhage, halitosis, and stomatitis; Rare: gastric

General Disorders and Administration Site Conditions - Frequent: chills/rigors; Infrequent: falls, feeling abnormal, feeling hot and/or cold, malaise, and thirst; Rare: Infections and Infestations — Infrequent: gastroenteritis and laryngitis. Investigations - Frequent: weight increased, weight decreased; Infrequent: blood cholesterol increased. Metabolism and Nutrition Disorders — Infrequent: dehydration and hyperlipidemia; Rare: dyslipidemia. Musculoskeletal and Connective Tissue Disorders - Frequent: musculoskeletal pain; Infrequent: muscle tightness and muscle twitching.

Nervous System Disorders - Frequent: dysgeusia, lethargy, and paraesthesia/hypoesthesia; Infrequent: disturbance in attention, dyskinesia, myoclonus, and poor

Psychiatric Disorders - Frequent: abnormal dreams and sleep disorder; Infrequent: apathy, bruxism, disorientation/confusional state, irritability, mood swings, and

Renal and Urinary Disorders — Frequent: urinary frequency; Infrequent: dysuria, micturition urgency, nocturia, polyuria, and urine odor abnormal. Reproductive System and Breast Disorders — Frequent: anorgasmia/orgasm abnormal; Infrequent: menopausal symptoms, sexual dysfunction, and testicular pain; Respiratory, Thoracic and Mediastinal Disorders — Frequent: yawning, oropharyngeal pain; Infrequent: throat tightness

Skin and Subcutaneous Tissue Disorders — Frequent: pruritus; Infrequent: cold sweat, dermatitis contact, erythema, increased tendency to bruise, night sweats, Vascular Disorders — Frequent: hot flush; Infrequent: flushing, orthostatic hypotension, and peripheral coldness. Adverse Reactions Observed in Placebo-Controlled Clinical Trials in Pediatric Patients Pediatric Clinical Trial Database The data described below reflect exposure to duloyetine delayed release cansules (N = 567) in pediatric natients and 7 to 18 years of ane from two 10 week, placeho. fibromyalgia (N = 91), Duloxetine delayed-release capsules are not approved for the treatment of MDD in pediatric patients (see Use in Specific Populations (8.4)). Of the

duloxetine delayed-release capsules-treated patients in these studies, 36% were 7 to 11 years of age (64% were between 12 to 18 years old), 55% were female, and 69% were Caucasian. Patients received 30 to 120 mg of duloxetine delayed-release capsules per day during placebo-controlled acute treatment studies. In the pediatric MDD, GAD, and fibromyalgia trials up to 40 weeks long, there were 988 duloxetine delayed release cansules treated pediatric natients aged 7 to 17 years of age (most natients received 30 to 120 mg per day) ·35% were 7 to 11 years of age (65% were 12 to 17 years old) and 56% were female Most Common Adverse Reactions in Pediatric Trials
The most common adverse reactions (≥5% in duloxetine delayed-release capsules-treated patients and at least twice the incidence of placebo-treated patients) in all pooled pediatric populations (MDD, GAD, and fibromyalgia) were decreased weight, decreased appetite, nausea, vomiting, fatigue, and diarrhea $\underline{Adverse\,Reactions\,in\,Pediatric\,Patients\,Aged\,7\,to\,17\,Years\,Old\,with\,MDD\,and\,GAD}$

The adverse reaction profile observed in clinical trials in pediatric patients aged 7 to 18 years old with MDD and GAD was consistent with the adverse reaction profile observed in adult clinical trials. The most common (\geq 5% and twice placebo) adverse reactions observed in these pediatric clinical trials included: nausea, diarrhea, decreased weight, and dizziness. Table 6 provides the incidence of adverse reactions in MDD and GAD pediatric placebo-controlled trials that occurred in greater than 2% of patients treated with duloxetine delayed-release capsules and with an incidence greater than patients treated with placebo. Duloxetine delayed-release capsules are not approved in the treatment of MDD

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

Oropharyngeal Pai Cough Duloxetine delayed-release capsules are not approved for the treatment of pediatric MDD /see Use in Specific Populations (8.4)/. The inclusion of an event in the table i determined based on the percentages before rounding; however, the percentages displayed in the table are rounded to the nearest integer

Also includes abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort, and gastrointestinal pain Frequency based on weight measurement meeting potentially clinically significant threshold of ≥ 3.5% weight loss (N=467 duloxetine delaved-release caosules: N=354 Also includes hypersomnia and sedation [†] Also includes initial insomnia, insomnia, middle insomnia, and terminal insomnia.

Other adverse reactions that occurred at an incidence of less than 2% and were reported by more duloxetine delayed-release capsules-treated patients than placebotreated patients in pediatric MDD and GAD clinical trials included: abnormal dreams (including nightmare), anxiety, flushing (including hot flush), hyperhidrosis, palpitations, pulse increased, and tremor (duloxetine delayed-release capsules are not approved to treat pediatric patients with MDD). The most commonly reported symptoms following discontinuation of duloxetine delayed-release capsules in pediatric MDD and GAD clinical trials included headache, dizziness, insomnia, and abdominal pain (see Warnings and Precautions (5.7)). Growth (Height and Weight) in Pediatric Patients 7 to 17 Years Old with GAD and MDD

Decreased appetite and weight loss have been observed in association with the use of SSRIs and SNRIs. Duloxetine delayed-release capsules-treated pediatric patients in clinical trials experienced a 0.1 kg mean decrease in weight at 10 weeks, compared with a mean weight gain of approximately 0.9 kg in placebo-treated pediatric patients. The proportion of patients who experienced a clinically significant decrease in weight (≥ 3.5%) was greater in the duloxetine delayed-release capsules group than in the placebo group (16% and 6%, respectively). Subsequently, over the 4- to 6-month uncontrolled extension periods, duloxetine delayed-release capsules-treated patients on average trended toward recovery to their expected baseline weight percentile based on population data from age- and sex-matched peers. In studies up to 9 months, duloxetine delayed-release capsules -treated pediatric patients experienced an increase in height of 1.7 cm on average (2.2 cm increase in patients 7 to 11 years of age and 1.3 cm increase in patients 12 to 17 years of age). While height increase was observed during these studies, a mean decrease of 1% in height percentile was observed (decrease of 2% in patients 7 to 11 years of age and increase of 0.3% in patients 12 to 17 years of age). Weight and height should be

nonitored regularly in pediatric patients treated with duloxetine delayed-release capsules [see Use in Specific Populations (8.4)]. Adverse Reactions in Pediatric Patients Aged 13 to 17 Years Old with Fibromyalgia Table 7 provides the incidence of adverse reactions in a fibromyalgia pediatric placebo-controlled trial (Study FM-4) that occurred in greater than 5% of patients treated with duloxetine delayed-release capsules and with an incidence greater than patients treated with placebo (see Clinical Studies (14.5))

able 7: Adverse Reactions: Incidence of 5% or More and Greater than Placebo in a 13-week Placebo-Controlled Trial in Pediatric Patients 13 to 17 Years Id with Fibromyalgia (Study FM-4)*			
	Duloxetine Hydrochloride (N=91)	Placebo (N = 93)	
Nausea	25%	15%	
Decreased appetite	15%	3%	
Vomiting	15%	5%	
Decreased weight ^b	15%	5%	
Headache	14%	11%	
Nasopharyngitis	9%	2%	
Somnolence	9%	3%	
Upper respiratory tract infection	7%	2%	
What anatomatoritie	E0/	Off/	

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 neares ' Frequency based on weight measurement meeting potentially clinically significant threshold of \geq 3.5% weight loss (N = 89 Duloxetine hydrochloride; N = 92 Placebo).

6.2 Postmarketing Experience The following adverse reactions have been identified during post approval use of duloxetine delayed release capsules. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Adverse reactions reported since market introduction that were temporally related to duloxetine delayed-release capsules therapy and not mentioned elsewhere in labeling include: acute pancreatitis, anaphylactic reaction, aggression and anger (particularly early in treatment or after treatment discontinuation), angioneurotic edema, angle-closure glaucoma, colitis (microscopic or unspecified), cutaneous vasculitis (sometimes associated with systemic involvement), extrapyramidal disorder, galactorrhea, gynecological bleeding, hallucinations, hyperglycemia, hyperprolactinemia, hypersensitivity, hypertensive crisis, muscle spasm, rash, restless legs syndrome, seizures upon treatment discontinuation, supraventricular arrhythmia, tinnitus (upon treatment discontinuation), trismus, and urticari

DRIIG INTERACTIONS Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism

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

7.9 Drugs Metabolized by CYP2D6

7.1 Inhibitors of CYP1A2 psules 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 t_{1/2} 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 (5.12).

7.2 Inhibitors of CYP2D6 Concomitant use of duloxetine delayed-release capsules (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 (5.12). 7.3 Dual Inhibition of CYP1A2 and CYP2D6 Concomitant administration of duloxetine delayed-release capsules 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 $C_{\rm max}$.

erotonin 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 to 9 mg once daily) under steady state conditions with duloxetine delayed-release capsules 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 varfarin (protein bound plus free drug) pharmacokinetics (AUC_{U.S.S.} C_{max.s} or t_{max.s.}) 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 delayed-release capsules are initiated or discontinued (see

Under steady-state conditions for duloxetine delayed-release capsules (60 mg Q. 12 hours) and lorazepam (2 mg Q. 12 hours), the pharmacokinetics of duloxetine were no affected by co-administration Under steady-state conditions for duloxetine delayed-release capsules (20 mg ghs) and temazepam (30 mg ghs), the pharmacokinetics of duloxetine were not affected by 7.7 Drugs that Affect Gastric Acidity

an earlier release of duloxetine. However, co.administration of duloxetine delayed release cansules with aluminum, and magnesium containing antacids (5.1 mFg) or exetine 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 (5.14)). 7.8 Druns Metabolized by CVP1A2 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, caffeinel 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% to 15%) and 20% (13% to 27%) when co-administered with duloxetine delayed-release capsules (60 mg twice daily).

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

50 mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold/see Warnings and Precautions (5.12)/. 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)).

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

 			 -
apsules and other bruising, especially if a non-steroidal anti- in.	apsules may cause his may need to be healthcare provider eeling rash, sores in	ine delayed-release Stopping duloxetine ther antidepressant	

mptoms may include: mptoms may include: agitation, hallucinations, coma or other changes in menta coordination problems or muscle twitching (overactive re racing heartbeat, high or low blood pressure sweating or fever nausea, vomiting, or diarrhea
muscle rigidity dizziness flushing tremor seizures seizures rressant medicines may increase your risk of bleeding or bruisi ke the blood thinner warfarin (Coumadin, Jantoven), a non natory drug (NSAIDs, like ibuprofen or naproxen), or aspirin.
were skin reactions: Duloxetine delayed-release capsul s skin reactions that may require stopping its use. This m d in a hospital and may be life-threatening. Call your health way or get emergency help if you have skin blisters, peeling uth, hives or any other allergic reactions.
scontinuation symptoms: Do not stop duloxetine di es without first talking to your healthcare provider. Stopp d-release capsules too quickly or changing from another a ickly may result in serious symptoms including: anxiety irritability
teeling tired or problems sleeping headache sweating dizziness electric shock-like sensations

sules wi ayed-rele quickly I e irrii e fee hez sw dizz away if you become pregnant or think ent with duloxetine delayed-release taking

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Duloxetine delayed-release capsules and other antidepressa medicines may increase suicidal thoughts or actions in son children, teenagers, or young adults within the first few months treatment or when the dose is changed.



2





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Ask you
Do not t
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How sh

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it away to r s, or feelings. Healthcare I

is in mood, behavior, actions, n changes. This is very important s started or when the dose is

se attention to any changes i , or feelings, especially sudden ch n antidepressant medicine is st

Depression and other serious men important causes of suicidal thoughts have a particularly high risk of having. These include people who have (or have a (also called manic-depressive illness).

How can I watch for and try to practions?

Pay close attention to any change thoughts, or feelings, especially sudde when an antidepressant medicine is changed.

Call your healthcare provider right changes in mood, behavior, thoughts, can be all follow-up visits with your healthcare provider betwee you have concerns about symptoms.

thoughts

prevent :

nner warfarin (Couma | anti-inflammatory c





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Call your healthcare provider right away if you have symptoms or feelings, especially if they are new, woo 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
• Other unusual changes in behavior or mood
• Other unusual changes in activity or talking in an antidepressant meeticine without first t provider. Stopping an antidepressant medicine suddle symptoms.

t first talking to a health e suddenly can cause c

What are duloxetine delayed-release capsules?

Duloxetine delayed-release capsules are a prescription medicine used to certain type of depression called Major Depressive Disorder (MDD). Du delayed-release capsules are belongs to a class of medicines known as S 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) Antidepressants are medicines used to treat depression It is important to discuss all the risks of treating deprisks of not treating it. Patients should discuss all tre your healthcare provider, not just the use of antidepress Antidepressant medicines have other side effects. Tal provider about the side effects of the medicine prescripmily member.

Antidepressant medicines can interact with other me

 Chronic Musculoskeletal Pain
 Who should not take duloxetine delayed-release capsules?
 Do Not take duloxetine delayed-release capsules?
 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 vourr hand. Who should bo Not take o

take duloxetine delayed-release capsules clasve a serious problem called Serotonin the possible side effects of duloxetine

What should I tell my healthcare provider delayed-release capsules?
Before starting duloxetine delayed-release cap

substrates is therefore not anticipated, although clinical studies have not been pe 7.13 Monoamine Oxidase Inhibitors (MAOIs)

[See Dosage and Administration (2.9, 2.10), Contraindications (4), and Warnings and Precautions (5.4)]. 7.14 Other Serotonergic Drugs

The concomitant use of serotonergic drugs (including other SNRIs, SSRIs, triptans, tricyclic antidepressants, opioids, lithium, buspirone, amphetamines, tryptophan, and St. John's Wort) with duloxetine increases the risk of serotonin syndrome. Monitor patients for signs and symptoms of serotonin syndrome, particularly during treatment initiation and dosage increases. If serotonin syndrome occurs, consider discontinuation of duloxetine and/or concomitant serotonergic drugs [see Warnings and Precautions (5.4)].

When duloxetine delayed-release capsules and ethanol were administered several hours apart so that peak concentrations of each would coincide, duloxetine delayedease capsules did not increase the impairment of mental and motor skills caused by alcohol In the duloxetine delayed-release capsules 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, 5.12)).

7.16 CNS Drugs [See Warnings and Precautions (5.12)]. 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 delayed-release capsules (60 or 120 mg) with warfarin (2 to 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)/. 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary rketing retrospective cohort study indicate that use of duloxetine in the month before delivery may be associated with an increased risk of postpartu hemorrhage. Data from published literature and from a postmarketing retrospective cohort study have not identified a clear drug-associated risk of major birth defects or other adverse developmental outcomes (see Data). There are risks associated with untreated depression and fibromyalgia in pregnancy, and with exposure to SNRIs and SSRIs, including duloxetine delayed-release capsules, during pregnancy (see Clinical Considerations). In rats and rabbits treated with duloxetine during the period of organogenesis, fetal weights were decreased but there was no evidence of developmental effects at doses up to 3 and 6 times, respectively, the maximum recommended human dose (MRHD) of 120 mg/day given to adolescents on a mg/m² basis. When duloxetine was administered orally to pregnant rats throughout gestation and lactation, pup weights at birth and pup survival to 1 day postpartum were decreased at a dose 2 times the MRHD given to adolescents on a mg/m² basis. At this dose, pup behaviors consistent with increased reactivity, such as increased startle response to noise and decreased

habituation of locomotor activity were observed. Post-weaning growth was not adversely affected. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively Clinical Considerations Women who discontinue antideoressants during pregnancy are more likely to experience a relanse of major degression than women who continue antideoressants. This

finding is from a prospective, longitudinal study that followed 201 pregnant women with a history of major depressive disorder who were euthymic and taking antidepressants at the beginning of pregnancy. Consider the risk of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum Pregnant women with fibromyalgia are at increased risk for adverse maternal and infant outcomes including preterm premature rupture of membranes, preterm birth, small for gestational age, intrauterine growth restriction, placental disruption, and venous thrombosis. It is not known if these adverse maternal and fetal outcomes are a direct result of fibromyalgia or other comorbid factors. Maternal Adverse Reactions

Use of duloxetine in the month before delivery may be associated with an increased risk of postpartum hemorrhage (see Warnings and Precautions (5.5)).

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

Data from a postmarketing retrospective claims-based cohort study found an increased risk for postpartum hemorrhage among 955 pregnant women exposed to duloxetine in the last month of pregnancy compared to 4, 128, 460 unexposed pregnant women (adjusted relative risk: 1.55; 95% Ct. 1.08-2.18). The same study did not find a clinically meaningful increase in the risk for major birth defects in the comparison of 2532 women exposed to duloxetine in the first trimester of pregnancy to 1,284,827 unexposed women after adjusting for several confounders. Methodologic limitations include possible residual confounding, misclassification of exposioutcomes, lack of direct measures of disease severity, and lack of information about alcohol use, nutrition, and over-the-counter medication exposures. In animal reproduction studies, duloxetine has been shown to have adverse effects on embryo/fetal and postnatal development.

When duloxetine was administered orally to pregnant rats and rabbits during the period of organogenesis, there was no evidence of malformations or developmental variations at doses up to 45 mg/kg/day [3 and 6 times, respectively, the MRHD of 120 mg/day given to adolescents on a mg/m² basis]. However, fetal weights were decreased at this dose, with a no-effect dose of 10 mg/kg/day (approximately equal to the MRHD in rats and 2 times the MRHD in rabbits). When duloxetine was administered orally to pregnant rats throughout gestation and lactation, the survival of pups to 1 day postpartum and pup body weights at birth and during the lactation period were decreased at a dose of 30 mg/kg/day (2 times the MRHD given to adolescents on a mg/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. 8.2 Lactation Risk Summary

Data from published literature report the presence of duloxetine in human milk (see Data). There are reports of sedation, poor feeding, and poor weight gain in infants exposed to duloxetine through breast milk (see Clinical Considerations). There are no data on the effect of duloxetine on milk productio The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for duloxetine delayed release cansules and any **Clinical Considerations** d-release capsules should be monitored for sedation, poor feeding and poor weight gair

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

The safety and effectiveness of duloxetine delayed-release cansules have been established for treatment of generalized anxiety disorder (GAD) in patients 7 to 17 years of age and for treatment of juvenile fibromyalgia syndrome in patients 13 to 17 years of age. The safety and effectiveness of duloxetine delayed-release capsules have not been established in pediatric patients with major depressive disorder (MDD), diabetic peripheral neuropathic pain, or chronic musculoskeletal pain. Antidepressants increased the risk of suicidal thoughts and behavior in pediatric patients. Monitor all pediatric patients being treated with antidepress worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of treatment, or at times of dosage changes (see Warnings and Precautions (5.1)]. Perform regular monitoring of weight and growth in pediatric patients treated with duloxetine delayed-release capsules (see Adverse Rea Generalized Anxiety Disorder Use of duloxetine delayed-release capsules for the treatment of GAD in patients 7 to 17 years of age is supported by one 10-week, placebo-controlled trial (GAD-6). The

study included 272 pediatric patients with GAD of which 47% were 7 to 11 years of age (53% were 12 to 17 years of age). Duloxetine delayed-release capsules demonstrated superiority over placebo as measured by greater improvement in the Pediatric Anxiety Rating Scale (PARS) for GAD severity score *[see Clinical Studies (14.3)]*. tine delayed-release capsules for the treatment of GAD in pediatric patients less than 7 years of age have not been e Use of dulaxetine delayed-release capsules for treatment of fibromyalgia in patients 13 to 17 years of age is supported by a 13-week placebo-controlled trial in 184 patients with juvenile fibromyalgia syndrome (Study FM-4). Duloxetine delayed-release capsules showed improvement over placebo on the primary endpoint, change from baseline to end-of-treatment on the Brief Pain Inventory (BPI) – Modified Short Form: Adolescent Version 24-hour average pain severity rating /see Clinical Studies (14.5)/.

The safety and effectiveness of duloxetine delayed-release capsules for the treatment of fibromyalgia in patients less than 13 years of age have not been established. Major Depressive Disorder The safety and effectiveness of duloxetine delayed-release capsules have not been established in pediatric patients for the treatment of MDD. Efficacy of duloxetine delayed-release capsules was not demonstrated in two 10-week, placebo-controlled trials with 800 pediatric patients aged 7 to 17 years old with MDD (MDD-6 and MDD-7). Neither duloxetine delayed-release capsules nor an active control (approved for treatment of pediatric MDD) was superior to placebo The most frequently observed adverse reactions in the MDD pediatric clinical trials included nausea, headache, decreased weight, and abdominal pain. Decreased appetite

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

8.5 Geriatric Use Geriatric Exposure in Premarketing Clinical Trials of Duloxetine Delayed-Release Capsules Of the 2,418 patients in MDD trials, 6% (143) were 65 years of age or over

Of the 1041 patients in CLBP trials, 21% (221) were 65 years of age or over Of the 487 patients in OA trials, 41% (197) were 65 years of age or over.

Of the 1,074 patients in the DPNP trials, 33% (357) were 65 years of age or over. Of the 1,761 patients in FM trials, 8% (140) were 65 years of age or over.

In the MDD, GAD, DPNP, FM, OA, and CLBP studies, no overall differences in safety or effectiveness were generally observed between these patients and younger adult.

patients, and other reported clinical experience has not identified differences in responses between these geriatric and younger adult patients, but greater sensitivity of SSRIs and SNRIs, including duloxetine delayed-release capsules have been associated with clinically significant hyponatremia in geriatric patients, who may be at greater risk for this adverse reaction [see Warnings and Precautions (5.13)]. $In an analysis of data from all place bo-controlled \cdot trials, duloxetine delayed \cdot release \ capsules \cdot treated \ patients \ reported \ a \ higher \ rate \ of falls \ compared \ to \ place bo-treated$

patients. The increased risk appears to be proportional to a patient's underlying risk for falls. Underlying risk appears to increase steadily with age. As geriatric patients tend to have a higher prevalence of risk factors for falls such as medications, medical comorbidities and gai disturbances, the impact of increasing age by itself on falls during duloxetine delayed-release capsules treatment is unclear. Falls with serious consequences including bone fractures and hospitalizations have been reported with duloxetine delayed-release capsules use (see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]. 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 C_{ms}, 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 adult patient is not necessary.

8.6 GenderDuloxetine's half-life is similar in men and women. Dosage adjustment based on gender is not necessary. 8.7 Smoking Status $ability \, (AUC) \, appears \, to \, be \, reduced \, by \, about \, one \cdot third \, in \, smokers. \, Do sage \, modifications \, are \, not \, recommended \, for \, smokers.$

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

8.9 Hepatic Impairment Patients with clinically evident hepatic impairment have decreased duloxetine metabolism and elimination. After a single 20 mg dose of duloxetine delayed-releas 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 (2.7) and Warnings and Precautions (5.14)]. 8.10 Severe Renal Impairment

Limited data are available on the effects of duloxetine delayed-release capsules in patients with end-stage renal disease (ESRD). After a single 60 mg dose of duloxetine delayed-release capsules, C.... and AUC values were approximately 100% greater in patients with ESRD receiving chronic intermittent hemodialysis than in subjects with normal renal function. The elimination half-life, however, was similar in both groups. The AUCs of the major circulating metabolites, 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate, largely excreted in urine, were approximately 7- to 9-fold higher and would be expected to increase further with multiple dosing. Population PK analyses suggest that mild to moderate degrees of renal impairment (estimated CrCl 30 to 80 mL/min) have no significant effect on duloxetine apparent clearance [see Dosage and Administration (2.7) and Warnings and Precautions (5.14)]. 9 DRUG ABUSE AND DEPENDENCE

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

10 OVERDOSAGE 10.1 Signs and Symptoms

9.2 Abuse

In drug dependence studies, duloxetine did not demonstrate dependence-producing potential in rats. In postmarketing experience, fatal outcomes have been reported for acute duloxetine delayed-release capsules overdoses, primarily with mixed overdoses, but also with duloxetine delayed-release capsules only, including 1000 mg of duloxetine delayed-release capsules (approximately 8.3 times the maximum recommended dosage). Signs and symptoms of overdose (duloxetine delayed-release capsules alone or with mixed drugs) included somnolence, coma, serotonin syndrome, seizures, syncope,

tachycardia, hypotension, hypertension, and vomiting, There is no specific antidote to a duloxetine delayed-release capsules overdosage, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine In case of acute overdose with duloxetine delayed-release capsules, treatment should consist of those general measures employed in the management of overdose with any drug, such as assuring an adequate airway, oxygenation, and ventilation and monitoring cardiac rhythm and vital signs. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Induction of emesis is not

Activated charcoal may be useful in limiting absorption of duloxetine from the gastrointestinal tract. Administration of activated charcoal has been shown to decrease Activated charcoan langue describ in initing absorption of universities from the gastionintestinan tract. Administration of activated charcoal language from the described in duloxetine for activated charcoal. Due to the large volume of distribution of duloxetine forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be beneficial. In managing overdose, the possibility of multiple drug involvement should be considered. A specific caution involves patients who overdose with duloxetine delayed-release cansules and tricyclic antidepressants. In such a case, decreased clearance of the parent tricyclic and/or its active metabolite may increase the possibility of clinically ignificant sequelae and extend the time needed for close medical observation [see Warnings and Precautions (5.4) and Drug Interactions (7]]. Consider contacting a poison control center (1-800-222-1222 or www.poison.org) for additional information on the treatment of overdosage 11 DESCRIPTION

Duloxetine delayed-release capsules, USP are a selective serotonin and norepinephrine reuptake inhibitor (SNRI) for oral administration. Its chemical designation is (yS)-N-Methyl-y-(1-napthalenyloxy)-2-thiophenepropanamine hydrochloride. The empirical formula is C_{iii}H_{is}NOS • HCI, which corresponds to a molecular weight of 333.87. The structural formula is:

Dulo yeting by drochloride. USP is an off-white to white colored crystalling nowder which is freely soluble in methanol and sparingly soluble in water Dubukenie rybucolinie, USF is an UFF-winter to winter consider crystalinie power winter is neery soluble in netranior and sparingly soluble in water. Each capsule contains film-coached pellets of 22.4, 33.7, or 67.3 mg of duboxetine hydrochloride, USP equivalent to 20, 30, or 60 mg of duboxetine, respectively. Inactive ingredients include crospovidone, FD & C Blue 2, gelatin, hydroxy propyl methyl cellulose acetate succinate, hypromellose, polyethylene glycol, polysorbate 80, sodium yl sulfate, sucrose, sugar spheres, talc, titanium dioxide and triethyl citrate. In addition, the 20 mg and 60 mg capsules also contain iron oxide yellow The imprinting ink contains propulene glucol, shellac, and strong ammonia solution. The 20 mg capsule also contains black iron oxide and potassium hydroxide. The 30 mg capsule also contains yellow iron oxide. The 60 mg capsule also contains potassium hydroxide and titanium dioxide. 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action related to its potentiation of serotonergic and noradrenergic activity in the CNS.

Duloxetine has no significant affinity for dopaminergic, adrenergic, cholinergic, histaminergic, opioid, glutamate, and GABA receptors in vitro. Duloxetine does not inhibit Duloxetine delayed-release capsules are in a class of drugs known to affect urethral resistance (see Warnings and Precautions (5.15)).

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

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

After oral duloxetine delayed-release capsules administration, duloxetine hydrochloride is well absorbed. There is a median 2 hour lag until absorption begins (T_{tap}), with maximal plasma concentrations (Cmax) of duloxetine occurring 6 hours post dose. There is a 3 hour delay in absorption and a one-third increase in apparent clearance of Effect of Food: Food does not affect the C_max of duloxetine, but delays the time to reach peak concentration from 6 to 10 hours and it marginally decreases the extent of

The apparent volume of distribution averages about 1640 L. Duloxetine is highly bound (>90%) to proteins in human plasma, binding primarily to albumin and α1-acid glycoprotein. The interaction between duloxetine and other highly protein bound drugs has not been fully evaluated. Plasma protein binding of duloxetine is not affected by renal or hepatic impairment.

ation and disposition of duloxetine in humans have been determined following oral administration of ¹⁴C-labeled duloxetine. Dulo the total radiolabeled material in the plasma, indicating that it undergoes extensive metabolism to numerous metabolites. The major biotransformation pathways for duloxetine involve oxidation of the naphthyl ring followed by conjugation and further oxidation. Both CYP1A2 and CYP2D6 catalyze the oxidation of the naphthyl ring in vitro. Metabolites found in plasma include 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate

Many additional metabolites have been identified in urine, some representing only minor pathways of elimination. Only trace (< 1% of the dose) amounts of unchanged duloxetine are present in the urine. Most fabout 70% of the duloxetine does appears in the urine as metabolites of duloxetine; about 20% is excreted in the faces.

Duloxetine undergoes extensive metabolism, but the major circulating metabolites have not been shown to contribute significantly to the pharmacologic activity of Specific Populations

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

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In female mice receiving duloxetine at 140 mg/kg/day (3 times the maximum recommended human dose (MRHD) of 120 mg/day given to children on a mg/m 2 basis), there was an increased incidence of hepatocellular adenomas and carcinomas. The no-effect dose was 50 mg/kg/day (1 time the MRHD given to children). Tumor incidence was not increased in male mice receiving duloyetine at doses up to 100 mg/kg/day (2 times the MRHD given to children) In rats, dietary doses of duloxetine up to 27 mg/kg/day in females (1 time the MRHD given to children) and up to 36 mg/kg/day in males (1.4 times the MRHD given to

vetine was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) and was not clastogenic in an *in vivo* chromosomal aberration test in m marrow cells. Additionally, duloxetine was not genotoxic in an *in vitro* mammalian forward gene mutation assay in mouse lymphoma cells or in an *in vitro*, unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, and did not induce sister chromatid exchange in Chinese hamster bone marrow *in viv* Impairment of Fertility

tine administered orally to either male or female rats prior to and throughout mating at doses up to 45 mg/kg/day (3 times the MRHD given to adolescents on a mg/m² hasis) did not alter mating or fertility.

14 CLINICAL STUDIES 14.1 Overview of the Clinical Trials The efficacy of duloxetine delayed-release capsules has been established in the following populations in adequate and well-controlled trials

Major Depressive Disorder (MDD): 4 short-term (Studies MDD-1, MDD-2, MDD-3, and MDD-4) and 1 maintenance trial (Study MDD-5) in adults /see Clinical Studies Generalized Anxiety Disorder (GAD): 3 short-term trials in adults (Studies GAD-1, GAD-2, and GAD-3), 1 maintenance trial in adults (Study GAD-4), 1 short-term Diabetic Peripheral Neuropathic Pain (DPNP): Two 12-week trials in adults (Studies DPNP-1 and DPNP-2)/see Clinical Studies (14.4)/.

Fibromyalgia (FM): Two trials in adults (one of 3 months duration and one of 6 months duration) (Studies FM-1 and FM-2) and one 13-week trial in pediatric patients 7 years of age (Study FM-4) /see Clinical Studies (14.5)]. Chronic Musculoskeletal Pain: Two 12- to 13-week trials in adult patients with chronic low back pain (CLBP) (Studies CLBP-1 and CLBP-3) and one 13-week trial in adult patients with chronic pain due to osteoarthritis (OA) (Study OA-1)/see Clinical Studies (14.6)]. Additionally, a summary of the following trials that did not demonstrate efficacy are presented below: Study FM-3 (a 16-week trial in adult patients with fibromyalgia). Study CLBP-2 (a 13-week trial in adult patients with CLBP), and Study OA-2 (a 13-week trial in adult patients with chronic pain due to OA 14.2 Major Depressive Disorder in Adults

The efficacy of duloxetine delayed-release capsules as a treatment for MDD in adults was established in 4 randomized, double-blind, placebo-controlled, fixed-dose trials in adult outpatients (18 to 83 years) meeting DSM-IV criteria for MDD: In Studies MDD-1 and MDD-2, patients were randomized to duloxetine delayed-release capsules 60 mg once daily (N = 123 and N = 128, respectively) or placebo (N = 122 and N = 139, respectively) for 9 weeks In Study MDD-3, patients were randomized to duloxetine delayed-release capsules 20 or 40 mg twice daily (N = 86 and N = 91, respectively) or placebo (N = 89) for 8

In Study MDD-4, patients were randomized to duloxetine delayed-release capsules 40 or 60 mg twice daily (N = 95 and N = 93, respectively) or placebo (N = 93) for 8 In all four trials, duloxetine delayed-release capsules demonstrated superiority over placebo as measured by improvement in the 17-item Hamilton Depression Rating Scale (HAMD-17) total score (see Table 8). There is no evidence that doses greater than 60 mg/day confer additional benefits. In all of these clinical trials, analyses of the relationship between treatment outcome and age, gender, and race did not suggest any differential responsiveness on the basis of these patient characteristics

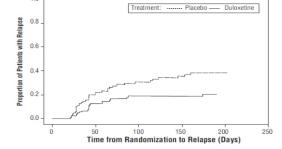
Table 8: Summary of the Primary Efficacy Results for Adult Trials in MDD

		Primary Efficacy Measure: HAMD-17			
Study Number	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference* (95% CI)	
Study MDD-1	Duloxetine Delayed-Release Capsules (60 mg/day) ^b	21.5 (4.10)	-10.9 (0.70)	-4.9 (-6.8, -2.9)	
	Placebo	21.1 (3.71)	-6.1 (0.69)		
Study MDD-2	Duloxetine Delayed-Release Capsules (60 mg/day) ^b	20.3 (3.32)	-10.5 (0.71)	-2.2 (-4.0, -0.3)	
	Placebo	20.5 (3.42)	-8.3 (0.67)		
Study MDD-3	Duloxetine Delayed-Release Capsules(20 mg BID) ^b	18.6 (5.85)	-7.4 (0.80)	-2.4 (-4.7, -0.2)	
	Duloxetine Delayed-Release Capsules(40 mg BID) ⁵	18.1 (4.52)	-8.6 (0.81)	-3.6 (-5.9, -1.4)	
	Placebo	17.2 (5.11)	-5.0 (0.81)		
Study MDD-4	Duloxetine Delayed-Release Capsules(40 mg BID) ^b	19.9 (3.54)	-11.0 (0.49)	-2.2 (-3.6, -0.9)	
	Duloxetine Delayed-Release Capsules(60 mg BID) ^b	20.2 (3.41)	-12.1 (0.49)	-3.3 (-4.7, -1.9)	
	Placebo	19.9 (3.58)	-8.8 (0.50)	-	

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval, not adjusted for multiplicity in trials where multiple dose groups were *Difference (drug minus placebo) in least-squares mean change from baseline Doses statistically significantly superior to placebo.

Figure 1: Cumulative Proportion of Adult Patients with MDD Relapse (Study MDD-5)

In Study MDD-5, 533 adult patients meeting DSM-IV criteria for MDD received duloxetine delayed-release capsules 60 mg once daily during an initial 12-week open-label treatment phase. Two hundred and seventy-eight patients who responded to open label treatment (defined as meeting the following criteria at weeks 10 and 12: a HAMD-7 total score < 9. Clinical Global Impressions of Severity (CGI-S) < 2. and not meeting the DSM-IV criteria for MDDI were randomly assigned to co duloxetine delayed-release capsules at the same dosage (N = 136) or to placebo (N = 142) for 6 months In Study MDD-5, patients on duloxetine delayed-release capsules experienced a statistically significantly longer time to relapse of depression than did patients on placebo (see Figure 1). Relapse was defined as an increase in the CGI-S score of \geq 2 points compared with that obtained at week 12, as well as meeting the DSM-IV criteria for MDD at 2 consecutive visits at least 2 weeks apart, where the 2-week temporal criterion had to be satisfied at only the second visit



*Kaplan-Meier estimator method. 14.3 Generalized Anxiety Disorder

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

In Studies GAD-1 and GAD-2, the starting dose was 60 mg once daily (down titration to 30 mg once daily was allowed for tolerability reasons; the dosage could be increased to 60 mg once daily). Fifteen percent of patients were down titrated. Study GAD-3 had a starting dose of 30 mg once daily for 1 week before increasing it to Studies GAD-2 and GAD-3 involved dose titration with duloxetine delayed-release capsules doses ranging from 60 mg once daily to 120 mg once daily (N = 168 and N=162) compared to placebo (N=159 and N=161) over a 10-week treatment period. The mean dosage for completers at endpoint in these trials was 104.8 mg/day. Study GAD-1 evaluated duloxetine delayed-release capsules dosages of 60 mg once daily (N=168) and 120 mg once daily (N=170) compared to placebo (N=175) over a 9-week treatment period. While a 120 mg/day dose was shown to be effective, there is no evidence that doses greater than 60 mg/day confer additional benefit. In all 3 trials, duloxetine delayed-release capsules demonstrated superiority over placebo as measured by greater improvement in the Hamilton Anxiety Scale (HAM-A) total score (see Table 8) and by the Sheehan Disability Scale (SDS) global functional impairment score. The SDS is a composite measurement of the extent emotional symptoms disrupt patient functioning in 3 life domains: work/school, social life/leisure activities, and family life/home responsibilities.

In Study GAD-4, 887 patients meeting DSM-IV-TR criteria for GAD received duloxetine delayed-release capsules 60 mg to 120 mg once daily during an initial 26-week open-label treatment phase. Four hundred and twenty-nine patients who responded to open-label treatment [defined as meeting the following criteria at weeks 24 and 26: a decrease from baseline HAM-A total score by at least 50% to a score no higher than 11, and a Clinical Global Impressions of Improvement (CGI-Improvement) score of 1 or 2] were randomly assigned to continuation of duloxetine delayed-release capsules at the same dosage (N=216) or to placebo (N=213) and were observed for relapse. Of the patients randomized, 73% had been in a responder status for at least 10 weeks. Relapse was defined as an increase in CGI-Severity score at least 2 points to a score ≥ 4 and a MINI (Mini-International Neuropsychiatric Interview) diagnosis of GAD (excluding duration), or discontinuation due to lack of efficacy. Patients taking duloxetine delayed-release capsules experienced a statistically significantly longer time to relapse of GAD than did patients taking placebo (see Figure 2). Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender

GAD Trial in Geriatric Patients e efficacy of duloxetine delayed-release capsules in the treatment of patients \geq 65 years of age with GAD was established in one 10-week flexible-dose, randomized, double-blind, placebo-controlled trial in adults \geq 65 years of age meeting the DSM-IV criteria for GAD (Study GAD-5). In Study GAD-5, the starting dose was 30 mg once daily for 2 weeks before further dose increases in 30 mg increments at treatment weeks 2, 4, and 7 up to 120 mg once daily were allowed based on investigator judgment of clinical response and tolerability. The mean dosage for patients completing the 10-week acute treatment phase was 51 mg. Patients treated with duloxetine delayedrelease capsules (N = 151) demonstrated significantly greater improvement compared with placebo (N = 140) on mean change from baseline to endpoint as measured by the HAM-A total score (see Table 8). GAD Trial in Pediatric Patients 7 to 17 Years Old The efficacy of duloxetine delayed-release capsules in the treatment of pediatric patients 7 to 17 years of age with GAD was established in 1 flexible-dose randomized,

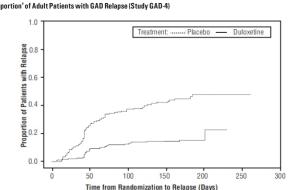
 $double-blind, place bo-controlled\ trial\ in\ pediatric\ outpatients\ with\ GAD\ (based\ on\ DSM-IV\ criteria)\ (Study\ GAD-6).$ In Study GAD-6, the starting dosage was 30 mg once daily for 2 weeks. Further dosage increases in 30 mg increments up to 120 mg once daily were allowed based on investigator judgment of clinical response and tolerability. The mean dosage for patients completing the 10-week treatment phase was 57.6 mg/day. In this study, duloxetine delayed-release capsules (N = 135) demonstrated superiority over placebo (N = 137) from baseline to endpoint as measured by greater improvement in the Pediatric Anxiety Rating Scale (PARS) for GAD severity score (see Table 9).

Table 9: Summary of the Primary Efficacy Results for GAD Trials

		Primary Efficacy Measure				
Study Number (population) (measurement)	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference* (95% CI)		
	Duloxetine Delayed-Release Capsules (60 mg/day) ^b	25.1 (7.18)	-12.8 (0.68)	-4.4 (-6.2, -2.5)		
Study GAD-1 (Adult) (HAM-A)	Duloxetine Delayed-Release Capsules (120 mg/day) ^b	25.1 (7.24)	-12.5 (0.67)	-4.1 (-5.9, -2.3)		
	Placebo	25.8 (7.66)	-8.4 (0.67)	**		
Study GAD-2	Duloxetine Delayed-Release Capsules (60 to 120 mg/day) ^b	22.5 (7.44)	-8.1 (0.70)	-2.2 (-4.2, -0.3)		
(Adult) (HAM-A)	Placebo	23.5 (7.91)	-5.9 (0.70)			
Study GAD-3	Duloxetine Delayed-Release Capsules (60 to 120 mg/day) ^b	25.8 (5.66)	-11.8 (0.69)	-2.6 (-4.5, -0.7)		
(Adult) (HAM-A)	Placebo	25.0 (5.82)	-9.2 (0.67)	**		
Study GAD-5 (Geriatric) (HAM-A)	Duloxetine Delayed-Release Capsules (60 to 120 mg/day) ^b	24.6 (6.21)	-15.9 (0.63)	-4.2 (-5.9, -2.5)		
	Placebo	24.5 (7.05)	-11.7 (0.67)	-		
Study GAD-6 (Pediatric) (PARS for GAD)	Duloxetine Delayed-Release Capsules (30 to 120mg/day) ^b	17.5 (1.98)	-9.7 (0.50)	-2.7 (-4.0, -1.3)		
	DI I	47.4 (0.04)	7.4 (0.50)	,		

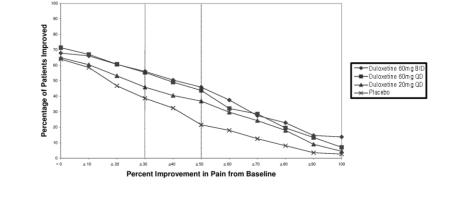
" Placebo 17.4 (2.24) -7.1 (0.50) SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval, not adjusted for multiplicity in trials where multiple dose groups were *Difference (drug minus placebo) in least squares mean change from baseline

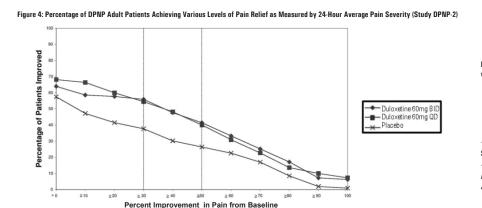
Figure 2: Cumulative Proportion of Adult Patients with GAD Relapse (Study GAD-4)



*Kaplan-Meier estimator method. 14.4 Diabetic Peripheral Neuropathic Pain in Adults The efficacy of duloxetine delayed release capsules for the management of neuropathic pain associated with diabetic peripheral neuropathy in adults was established in 2 randomized, 12-week, double-blind, placebo-controlled, fixed-dose trials in adult patients having diabetic peripheral neuropathic pain (DPNP) for at least 6 months (Study DPNP-1). These trials enrolled a total of 791 patients of whom 592 (75%) completed the trials. Patients enrolled had Type I or II diabetes mellitus with a diagnosis of painful distal symmetrical sensorimotor polyneuropathy for at least 6 months. The patients had a baseline pain score of ≥ 4 on an 11-point scale ranging from O (no pain) to 10 (worst possible pain). Patients were permitted up to 4 grams of acetaminophen per day as needed for pain, in addition to dulo: capsules. Patients recorded their pain daily in a diary.

Both trials compared duloxetine delayed-release capsules 60 mg once daily or 60 mg twice daily with placebo. Study DPNP-1 additionally compared duloxetine delayedrelease capsules 20 mg with placebo. A total of 457 patients (342 duloxetine delayed-release capsules, 115 placebo) were enrolled in Study DPNP-1 and a total of $334\,patients\,(226\,duloxetine\,delayed\text{-}release\,capsules,\,108\,placebo)\,were\,enrolled\,in\,Study\,DPNP\cdot 2.$ reatment with duloxetine delayed-release capsules 60 mg one or two times a day statistically significantly improved the endpoint mean pain scores from baseline an tion of patients with at least a 50% reduction in pain scores from baseline. For vario Figures 3 and 4 show the fraction of patients achieving that degree of improvement in Studies DPNP-1 and DPNP-2, respectively. The figures are cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the trial were assigned 0% improvement. Some patients experienced a decrease in pain as early as week 1, which persisted throughout the trial. Figure 3: Percentage of DPNP Adult Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study DPNP-1

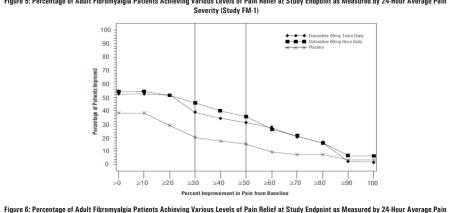


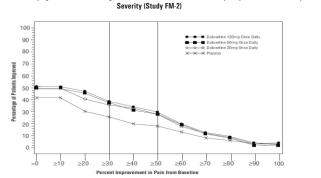


Adult Trials in Fibromyalgia he efficacy of duloxetine delayed-release capsules for the management of fibromyaloia in adults was established in two randomized, double-blind, placebo-controlled. fixed-dose trials in adult nationts meeting the American College of Rheumatology criteria for fibromyalgia (a history of widespread pain for 3 months, and pain present at inservouse trais in autop patients meaning the Amientana Connege of miscinary or instrumy of miscary or wirespiear pain for 3 mismas, and pain present of 11 or more of the 18 specific tender point sites). Study FM-1 was shree months in duration and enrolled female patients only. Study FM-2 was sty months in duration and enrolled female patients only. Study FM-1 was sty months in duration and enrolled female patients only. Study FM-1 was sty months in duration and enrolled female patients only. Study FM-2 was sty months in duration and enrolled female patients only. Study FM-2 was sty months in duration and enrolled female patients only. Study FM-1 was stylength on the stylength of the stylength 541 (62%) completed the trials. A total of 354 patients (234 duloxetine delayed-release capsules, 120 placebo) were enrolled in Study FM-1 and a total of 520 patients (376 duloxetine delayed-release capsules, 144 placebo) were enrolled in Study FM-2 (5% male, 95% female). The patients had a baseline pain score of 6.5 on an 11-point

14.5 Fibromyalgia

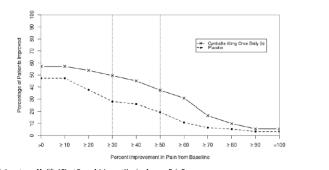
scale ranging from 0 (no pain) to 10 (worse possible pain). lies FM-1 and FM-2 compared duloxetine delayed-release capsules 60 mg once daily or 120 mg daily (given in divided doses in Study FM-1 and as a single daily dose in Study FM-2) with placeho. Study FM-2 additionally compared duloxetine delayed release capsules 20 mg with placeho during the initial three months of a six-month trial. Treatment with duloxetine delayed-release capsules 60 mg or 120 mg daily statistically significantly improved the endpoint mean pain scores from baseline and increased the proportion of patients with at least a 50% reduction in pain score from baseline. Pain reduction was observed in patients both with and without comorbid MDD. However, the degree of pain reduction may be greater in patients with comorbid MDD. For various degrees of improvement in pain from baseline to study endpoint, Figures 5 and 6 show the fraction of patients achieving that degree of improvement in Studies FM-1 and FM-2, respectively. The figures are cumulative so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the trial were assigned 0% improvement. Some patients experienced a decrease in pain as early as week 1, which persisted throughout the trial. Improvement was also demonstrated on measures of function (Fibromyalgia Impact Questionnaires) and patient global impression of change (PGI). Neither trial demonstrated a benefit of 120 mg compared to 60 mg, and a Figure 5: Percentage of Adult Fibromyalgia Patients Achieving Various Levels of Pain Relief at Study Endpoint as Measured by 24-Hour Average Pain





Additionally, the benefit of up-titration in non-responders to duloxetine delayed-release capsules at 60 mg/day was evaluated in a separate trial (Study FM-3). Adult patients were initially treated with duloxetine delayed-release capsules 60 mg once daily for eight weeks in open-label fashion. Subsequently, completers of this phase were randomized to double-blind treatment with duloxetine delayed-release capsules at either 60 mg once daily or 120 mg once daily. Responders were defined as patients who had at least a 30% reduction in pain score from baseline at the end of the 8-week treatment. Patients who were non-responders at 8 weeks were no more likely to meet response criteria at the end of 60 weeks of treatment if blindly titrated to duloxetine delayed-release capsules 120 mg as compared to those who were blindly continued on duloxetine delayed-release cansules 60 mg.

Pediatric Trial in Fibromyalgia Duloxetine delayed-release capsules was studied in 184 pediatric patients aged 13 to 17 years with juvenile fibromyalgia syndrome in a 13-week, placebo-controlled trial (Study FM-4). In Study FM-4, 149 (81%) patients completed the trial. Duloxetine delayed-release capsules (N = 91) was initiated at a dosage of 30 mg once daily for one week and titrated to 60 mg once daily for 12 weeks, as tolerated. The mean dosage for patients completing the 12-week treatment phase was 49 mg/day. Duloxetine delayed-release capsules showed improvement over placebo on the primary endpoint [change from baseline to end-of-treatment on the Brief Pain Inventory (BPI) – Modified Short Form: Adolescent Version 24-hour average pain severity rating) with a p-value of 0.052 from the prespecified primary analysis, and p-values ranging from 0.011 to 0.020 from sensitivity analyses which assigned baseline values to missing assessments of some patients who did not complete the trial for various reasons. The patients had a baseline BPI of 5.7. For various degrees of improvement in pain from baseline to study endpoint, Figure 7 shows the fraction of patients achieving that Figure 7: Percentage of Pediatric Patients Aged 13 to 17 Years Old with Juvenile Fibromyalgia Syndrome Achieving Various Levels of Pain Relief at Week



*Pain relief Measured by Brief Pain Inventory - Modified Short Form: Adolescent Version Average Pain Score tine delayed-release capsules-treated patients received 30 mg once daily for 1 week and subsequently titrated to 60 mg once daily for 12 weeks, as tolerated. 14.6 Chronic Musculoskeletal Pain in Adults Duloxetine delayed-release capsules are indicated for the treatment of chronic musculoskeletal pain in adults. This has been established in trials in adult patients with

Trials in Chronic Low Back Pain in Adults The efficacy of duloxetine delayed-release capsules in chronic low back pain (CLBP) in adults was assessed in two double-blind, placebo-controlled, randomized clinical trials of 13-weeks duration (Studies CLBP-1 and CLBP-2), and one of 12-weeks duration (CLBP-3). Studies CLBP-1 and CLBP-3 demonstrated efficacy of duloxetine capsules in the treatment of CLBP. Patients in all trials had no signs of radiculopathy or spinal stenosis Study CLBP-1: Two hundred thirty-six adult patients (N = 115 on duloxetine delayed-release capsules, N = 121 on placebo) enrolled and 182 (77%) completed 13-week treatment phase. After 7 weeks of treatment, duloxetine delayed-release capsules-treated patients with less than 30% reduction in average daily pain and who were able to tolerate 60 mg once daily had their duloxetine delayed-release capsules dosage, in a double-blinded fashion, increased to 120 mg once daily for the remainder of the trial. Patients had a mean baseline pain rating of 6 on a numerical rating scale ranging from 0 (no pain) to 10 (worst possible pain). After 13 weeks of treatment, patients taking duloxetine delayed-release capsules 60 to 120 mg daily had a significantly greater pain reduction compared to patients taking placebo. Randomization was stratified by the patients' baseline NSAIDs use status. Subgroup analyses did not indicate that there were differences in treatment outcomes as a function of NSAIDs use. Study CLBP-2: Four hundred and four patients were randomized to receive fixed dosages of duloxetine delayed-release capsules daily or a matching placebo (N = 59 on duloxetine delayed-release capsules 20 mg, N = 116 on duloxetine delayed-release capsules 60 mg, N = 112 on duloxetine delayed-release capsules 120 mg, N = 117 on placebo) and 267 (66%) completed the entire 13-week trial. After 13 weeks of treatment, none of the three duloxetine delayed-release capsules dosages showed a

statistically significant difference in pain reduction compared to placebo. Study CLBP-3: Four hundred and one patients were randomized to receive fixed doses of duloxetine delayed-release capsules 60 mg daily or placebo (N = 198 on duloxetine delayed-release capsules, N = 203 on placebo), and 303 (76%) completed the trial. Patients had a mean baseline pain rating of 6 on a numerical rating scale ranging from 0 (no pain) to 10 (worst possible pain). After 12 weeks of treatment, patients taking duloxetine delayed-release capsules 60 mg daily had significantly greater pain reduction compared to patients taking placebo. For various degrees of improvement in pain from baseline to study endpoint, Figures 8 and 9 show the fraction of patients in Studies CLBP-1 and CLBP-3 achieving that

degree of improvement, respectively. The figures are cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the trial were assigned the value of 0% improvement Figure 8: Percentage of Adult Patients with CLBP Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study

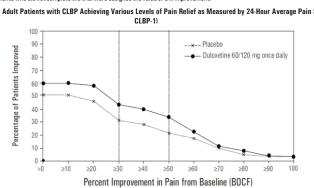
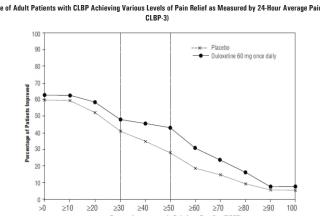


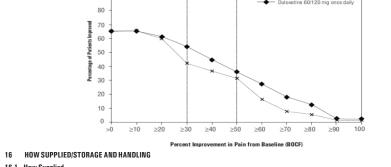
Figure 9: Percentage of Adult Patients with CLBP Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study



Trials in Chronic Pain Due to Osteoarthritis in Adults The efficacy of duloxetine delayed-release capsules in chronic pain due to osteoarthritis (OA) in adults was assessed in 2 double-blind, placebo-controlled, randomized clinical trials of 13-weeks duration (Study OA-1 and Study OA-2). All patients in both trials fulfilled the ACR clinical and radiographic criteria for classification of idiopathic OA of the knee. Randomization was stratified by the patients' baseline NSAIDs-use status. Patients assigned to duloxetine delayed-release capsules started treatment in both trials at a dose of 30 mg once daily for one week. After the first week, the dose of

duloxetine delayed-release capsules was increased to 60 mg once daily. After 7 weeks of treatment with duloxetine delayed-release capsules 60 mg once daily, in Study 0A-1 patients with sub-optimal response to treatment (< 30% pain reduction) and tolerated duloxetine delayed-release capsules 60 mg once daily had their dose increased to 120 mg. However, in Study OA-2, all patients, regardless of their response to treatment after 7 weeks, were re-randomized to either continue receiving duloxetine delayed-release capsules 60 mg once daily or have their dosage increased to 120 mg once daily for the remainder of the trial. Patients in the placebo treatment groups in both trials received a matching placebo for the entire duration of trials. For both trials, efficacy analyses were conducted using 13-week data from the combined duloxetine delayed-release capsules 60 mg and 120 mg once daily treatment groups compared to the placebo group. Study OA-1: Two hundred fifty-six patients (N = 128 on duloxetine delayed-release capsules, N = 128 on placebo) enrolled and 204 (80%) completed the trial. Patients had a mean baseline pain rating of 6 on a numerical rating scale ranging from 0 (no pain) to 10 (worst possible pain). After 13 weeks of treatment, patients taking duloxetine delayed-release capsules had significantly greater pain reduction than patients taking placebo. Subgroup analyses did not indicate that there were differences in treatment outcomes as a function of NSAIDs use. Study OA-2: Two hundred thirty-one patients (N = 111 on duloxetine delayed-release capsules, N = 120 on placebo) enrolled and 173 (75%) completed the trial. Patients had a mean baseline pain of 6 on a numerical rating scale ranging from 0 (no pain) to 10 (worst possible pain). After 13 weeks of treatment, patients taking duloxetine delayed-release capsules did not show a significantly greater pain reduction than patients taking placebo.

In Study OA-1, for various degrees of improvement in pain from baseline to study endpoint, Figure 10 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the trial were assigned the value of 0% improvement. Figure 10: Percentage of Adult Patients with OA Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity (Study OA-1)

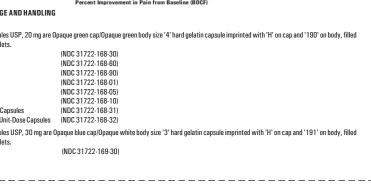


with white to off white colored pellets. Bottles of 30 Cansules (NDC 31722-168-30) Bottles of 60 Capsules

Bottles of 90 Capsules (NDC 31722-168-90) Bottles of 100 Capsule (NDC 31722-168-01) (NDC 31722-168-05) Bottles of 500 Capsules Bottles of 1000 Capsules (NDC 31722-168-10) Blister Card of 7 Unit-Dose Capsules (NDC 31722-168-31) Blister Pack of 105 (15x7) Unit-Dose Capsules (NDC 31722-168-32)

16.1 How Supplied

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 '191' on body, filled with white to off white colored pellets.



(NDC 31722-169-90) Bottles of 90 Capsules Bottles of 100 Capsules (NDC 31722-169-01 Bottles of 1000 Capsule (NDC 31722-169-10 Blister Card of 7 Unit-Dose Capsules (NDC 31722-169-31) Blister Pack of 105 (15x7) Unit-Dose Cansules (NDC 31722-169-32) Duloxetine Delayed-Release Capsules USP, 60 mg are Opaque blue cap/Opaque green body size '1' hard gelatin capsule imprinted with 'H' on cap and '192' on body, filled with white to off white colored pellets. (NDC 31722-170-30) Bottles of 30 Capsules Rottles of 90 Capsules (NDC 31722-170-90 (NDC 31722-170-01) Bottles of 100 Capsules Bottles of 1000 Capsules (NDC 31722-170-10) Blister Pack of 90 (9x10) Unit-Dose Capsules (NDC 31722-170-32) 16.2 Storage and Handling Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION $\label{lem:def} \textbf{Advise the patient to read the FDA-approved patient labeling (Medication Guide)}.$ Suicidal Thoughts and Behaviors - Advise patients, their families, and their caregivers to look for the emergence of suicidal ideation and behavior, especially during treatment and when the dose is adjusted up or down and instruct them to report such symptoms to their healthcare provider (see Boxed Warning and Warnings and Precautions (5.1)1. Administration - Advise patients to swallow duloxetine delayed-release capsules whole and to not chew, crush, or open the capsule (do not sprinkle contents on od or mixed with liquids) because these actions might affect the enteric coating.

Hepatotoxicity - Inform patients that severe liver problems, sometimes fatal, have been reported in patients treated with duloxetine delayed-release capsules. Instruct patients to talk to their healthcare provider if they develop itching, right upper belly pain, dark urine, or yellow skin/eyes while taking duloxetine delayedrelease capsules, which may be signs of liver problems. Instruct patients to talk to their healthcare provider about their alcohol consumption. Use of duloxetine layed-release capsules with heavy alcohol intake may be associated with severe liver injury (see Warnings and Precautions (5.2)) Alcohol - Although duloxetine delayed-release capsules does not increase the impairment of mental and motor skills caused by alcohol, use of duloxetine delayedrelease capsules concomitantly with heavy alcohol intake may be associated with severe liver injury (see Warnings and Precautions (5,2) and Drug Interactions

Orthostatic Hypotension, Falls and Syncope - Advise patients of the risk of orthostatic hypotension, falls and syncope, especially during the period of initial use and subsequent dose escalation, and in association with the use of concomitant drugs that might potentiate the orthostatic effect of duloxetine delayed-release capsules (see Warnings and Precautions (5.3)). Serotonin Syndrome - Caution patients about the risk of serotonin syndrome with the concomitant use of duloxetine delayed-release capsules and other serotonergic servoim symbols: - Caution parties about the isk or servoim symbols even to uncomman use or unionsemble even executions and other servoimengue, agents including triplans, tricyclic antidepressants, opioids, lithium, buspirone, tryptophan, ampheramines, and \$1.0 bin's Wort/see Contraindications (4). Warnings and Precautions (5.4), and Drug Interactions (7.14). Advise patients of the signs and symptoms associated with servoinin syndrome that may include mental status changes

(e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia neuromuscular changes (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Caution patients to seek medical care immediately if they experience these symptoms. Increased Risk of Bleeding - Caution patients about the concomitant use of duloxetine delayed-release capsules and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding /see Warnings and Precautions (5.5) and Use in Specific Populations (8.1)].

Severe Skin Reactions - Caution patients that duloxetine delayed-release capsules may cause serious skin reactions. This may need to be treated in a hospital and may be life-threatening. Counsel patients to call their doctor right away or get emergency help if they have skin blisters, peeling rash, sores in their mouth, hives, or any other allergic reactions (see Warnings and Precautions (5.6)). Discontinuation of Treatment - Instruct patients that discontinuation of duloxetine delayed-release capsules may be associated with symptoms such as dizziness, headache, nausea, diarrhea, paresthesia, irritability, vomiting, insomnia, anxiety, hyperhidrosis, and fatigue, and should be advised not to alter their dosing regimen, or stop taking duloxetine delayed-release capsules without consulting their healthcare provider [see Warnings and Precautions (5.7)]. Activation of Mania or Hypomania - Adequately screen patients with depressive symptoms for risk of bipolar disorder (e.g., family history of suicide, bipolar

sorder, and depression) prior to initiating treatment with duloxetine delayed-release capsules. Advise patients to report any signs or symptoms of a manic reaction such as greatly increased energy, severe trouble sleeping, racing thoughts, reckless behavior, talking more or faster than usual, unusually grand ideas, and happiness or irritability (see Warnings and Precautions (5.8)). Angle-Closure Glaucoma - Advise patients that taking duloxetine delayed-release capsules can cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle-closure glaucoma. Pre-existing glaucoma is almost always open-angle glaucoma because angle-closure glaucoma, when diagnosed, can be treated definitively with iridectomy. Open-angle glaucoma is not a risk factor for angle-closure glaucoma. Patients may wish to be examined to determine whether they are susceptible to angle-closure, and have a prophylactic procedure (e.g., iridectomy), if they are susceptible [see Warnings and Precautions (5.9]]. Seizures - Advise patients to inform their healthcare provider if they have a history of seizure disorder (see Warnings and Precautions (5.10)).

Concomitant Medications - Advise patients to inform their healthcare provider if they are taking, or plan to take, any prescription or over-the-counter medications, since there is a potential for interactions (see Dosage and Administration (2.9, 2.10), Contraindications (4), Warnings and Precautions (5.4, 5.12), and Drug <u>Hyponatremia</u> - Advise patients that hyponatremia has been reported as a result of treatment with SNRIs and SSRIs, including duloxetine delayed-release capsules. Advise patients of the signs and symptoms of hyponatremia Concomitant Illnesses - Advise patients to inform their healthcare provider about all of their medical conditions [see Warnings and Precautions (5.14)]. Urinary Hesitation and Retention - Duloxetine delayed-release capsules are in a class of medicines that may affect urination. Instruct patients to consult with their healthcare provider if they develop any problems with urine flow (see Warnings and Precautions (5.15)).

Effects on Blood Pressure - Caution patients that duloxetine delayed-release capsules may cause an increase in blood pressure (see Warnings and Precautions

Sexual Dysfunction - Advise patients that use of duloxetine delayed-release capsules may cause symptoms of sexual dysfunction in both male and female patients. Inform patients that they should discuss any changes in sexual function and potential management strategies with their healthcare provider (see Warnings and Pregnancy Advise women to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with duloxetine delayed-release Advise pregnant women or patients who intend to become pregnant that duloxetine delayed-release capsules may increase the risk of neonatal

complications requiring prolonged hospitalization, respiratory support, and tube feeding.

 Advise pregnant women that there is a risk of relanse with discontinuation of antidepressants. Lactation - Advise breastfeeding women using duloyetine delayed-release cansules to monitor infants for sedation, noor feeding and noor weight gain and to seek medical care if they notice these signs [see Use in Specific Populations (8.2)]. Interference with Psychomotor Performance - Duloxetine delayed-release capsules may be associated with sedation and dizziness. Therefore, caution patients about operating hazardous machinery including automobiles, until they are reasonably certain that duloxetine delayed-release capsules therapy does not affect their ability to engage in such activities.



Piscataway, NJ 08854

Manufactured by: HETERO™ HETERO LABS LIMITED Hyderabad - 500 055, India

Revised: 06/2024

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Call your doctor for medical advice at side effects to 1-800-FDA-1088.

How should I store duloxetine delayedStore duloxetine delayed-release capsules to 77°F (20°C to 25°C). 1°86

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