Product Monograph

Including Patient Medication Information

[Pr]AG-Duloxetine

Duloxetine Delayed-Release Capsules

Capsule (delayed-release)

For oral use

30 mg and 60 mg (duloxetine as duloxetine hydrochloride)

Manufacturer's standard

Analgesic/Antidepressant/Anxiolytic

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Recent Major Label Changes

3 Serious Warnings and Precautions Box	2026-09
7 Warnings and Precautions, Reproductive Health: Function	2026-09

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Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

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Part 1: Healthcare Professional Information

1 Indications

AG-Duloxetine (duloxetine delayed-release capsule) is indicated in adults for:

- Major Depressive Disorder

AG-Duloxetine is indicated for the symptomatic relief of major depressive disorder (MDD).

The efficacy of duloxetine delayed-release capsules in maintaining an antidepressant response for up to 12 months in patients who have shown initial treatment response following up to 34 weeks of open-label acute treatment was demonstrated in 2 placebo-controlled trials.

The efficacy of duloxetine delayed-release capsules in hospitalized patients with MDD has not been studied.

- Generalized Anxiety Disorder

AG-Duloxetine is indicated for the symptomatic relief of anxiety causing clinically significant distress in patients with generalized anxiety disorder (GAD).

The efficacy of duloxetine delayed-release capsules in maintaining anxiolytic response for up to 6 months in patients with GAD was demonstrated in a long-term placebo-controlled trial in patients who had initially responded to duloxetine delayed-release capsules during a 6-month open-label phase.

- Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

AG-Duloxetine is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN).

- Fibromyalgia

AG-Duloxetine is indicated for the management of pain associated with fibromyalgia (FM).

- Chronic Low Back Pain

AG-Duloxetine is indicated for the management of chronic low back pain (CLBP).

- Osteoarthritis of the Knee

AG-Duloxetine is indicated for the management of chronic pain associated with osteoarthritis (OA) of the knee.

Long-Term Use of AG-Duloxetine

The efficacy of duloxetine delayed-release capsules in long-term use for MDD has been demonstrated in controlled clinical trials for up to 12 months. Healthcare professionals should periodically re-evaluate the long-term usefulness of AG-Duloxetine for the individual patient.

The efficacy of duloxetine delayed-release capsules has been demonstrated in controlled clinical trials for up to 12 weeks in DPN and FM and up to 13 weeks in patients with CLBP and OA. The healthcare professional who elects to use AG-Duloxetine for extended periods in DPN, FM, CLBP or OA should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

1.1 Pediatrics

Pediatrics (<18 years of age): Health Canada has not authorized an indication for pediatric use. (see 3 Serious Warnings and Precautions Box and 7 Warnings and Precautions: Pediatrics).

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Pharmacokinetic results suggest no overall differences between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. (see 7.1.4 Geriatrics and 10.3 Pharmacokinetics: Special Populations and Conditions).

2 Contraindications

- Hypersensitivity – AG-Duloxetine (duloxetine delayed-release capsules) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medical ingredient, or component of the container. (For a complete listing of the ingredients, see 6 Dosage Forms, Strengths, Composition and Packaging).
- Monoamine Oxidase Inhibitors (MAOIs) – AG-Duloxetine should not be used concomitantly with a monoamine oxidase inhibitor (MAOI), including the antibiotic linezolid and the thiazine dye methylthioninium chloride (methylene blue) which are less well-known examples of MAOIs, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping AG-Duloxetine before starting an MAOI. (see 9.1 Serious Drug Interactions).
- Hepatic Impairment – AG-Duloxetine is contraindicated in patients with any liver disease resulting in hepatic impairment. (see 7 Warnings and Precautions: Hepatic/Biliary/Pancreatic: Hepatic Impairment; and 4 Dosage And Administration: General Considerations for Dosing in Special Populations).

- Uncontrolled Narrow-Angle Glaucoma - In clinical trials, duloxetine delayed-release capsules was associated with an increased risk of mydriasis; therefore, its use should be avoided in patients with uncontrolled narrow-angle glaucoma. (see 7 Warnings and Precautions: Ophthalmologic).
- Severe Renal Impairment – AG-Duloxetine is contraindicated in patients with severe renal impairment (i.e. creatinine clearance <30 mL/min) or end-stage renal disease. (see 7 Warnings and Precautions: Renal).
- Thioridazine - Concomitant use of AG-Duloxetine and thioridazine is contraindicated. (see 9.1 Serious Drug Interactions).
- CYP1A2 Inhibitors- Duloxetine should not be used concomitantly with potent CYP1A2 inhibitors (e.g. fluvoxamine) and some quinolone antibiotics (e.g. ciprofloxacin or enoxacin). (see 9.1 Serious Drug Interactions).

3 Serious Warnings and Precautions Box

Serious Warnings and Precautions

Suicidal thoughts and behaviour: Antidepressants increased the risk of suicidal thoughts and behaviour in pediatric and young adult patients in short-term clinical trials. Closely monitor all antidepressant-treated patients for clinical worsening and for emergence of agitation type and/or suicidal thoughts and behaviors. AG-Duloxetine (duloxetine delayed-release capsules) is not indicated for pediatric use (see 7 Warnings and Precautions: Psychiatric and 7.1.3 Pediatrics)

4 Dosage and Administration

4.1 Dosing Considerations

Switching Patients to or from a Monoamine Oxidase Inhibitor: At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with AG-Duloxetine. In addition, at least 5 days should be allowed after stopping AG-Duloxetine before starting an MAOI (see 2 Contraindications: MAOIs and 9.1 Serious Drug Interactions).

Patients with Hepatic or Renal Impairment: AG-Duloxetine is contraindicated in patients with severe renal impairment or with any liver disease resulting in hepatic impairment (see 2 Contraindications and 4.2 Recommended Dose and Dosage Adjustment). AG-Duloxetine should only be used in exceptional circumstances and with extreme caution in patients who consume substantial amounts of alcohol (see 7 Warnings and Precautions: Hepatic/Biliary/Pancreatic).

Pregnant Women: AG-Duloxetine should not be used during pregnancy unless the benefits markedly outweigh the risks, particularly during the third trimester as there are implications for neonatal health (see 7.1.1 Pregnancy and 4.2 Recommended Dose and Dosage Adjustment).

CYP1A2 Inhibitors- Concomitant of AG-Duloxetine with potent CYP1A2 inhibitors (e.g. fluvoxamine) and some quinolone antibiotics (e.g. ciprofloxacin or enoxacin) is contraindicated (see 2 Contraindications, 9.1 Serious Drug Interactions and 9.4 Drug-Drug Interactions).

Long-term treatment: Patients should be periodically re-assessed to determine the need to continue treatment (see 4.2 Recommended Dose and Dosage Adjustment).

4.2 Recommended Dose and Dosage Adjustment

Adults:

Major Depressive Disorder

The recommended dose is 60 mg once daily. A lower starting dose of 30 mg may be considered for tolerability reasons in some patients, with a target dose of 60 mg/day within 1-2 weeks. Therapeutic response is usually seen after 1-4 weeks of treatment. There is no evidence that doses greater than 60 mg/day confer additional benefit (see 14 Clinical Trials).

Generalized Anxiety Disorder

The recommended dose is 60 mg once daily. A lower starting dose of 30 mg may be considered for tolerability reasons in some patients, with a target dose of 60 mg/day within 1-2 weeks (see Dosage for Elderly Patients). Therapeutic response is usually seen after 1-4 weeks of treatment. While a 120 mg once daily dose was shown to be safe and effective, there is no evidence that doses greater than 60 mg/day confer additional benefit and the higher dose is less well tolerated. Daily doses above 120 mg have not been evaluated for safety or efficacy and are not recommended (see 14 Clinical Trials).

Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

The recommended dose is 60 mg once daily. A lower starting dose of 30 mg may be considered for tolerability reasons in some patients, with a target dose of 60 mg/day within 1-2 weeks. Efficacy of duloxetine delayed-release capsules has been demonstrated within the first week.

Some patients may benefit from dosages above the recommended 60 mg once daily up to a maximum dose of 120 mg per day. While a 120 mg/day dose was shown to be safe and effective, there is no evidence that doses greater than 60 mg/day confer additional significant benefit, and the higher dose is less well tolerated (see 8 Adverse Reactions, Table 4). Daily doses above 120 mg have not been evaluated for safety or efficacy and are not recommended (see 14 Clinical Trials).

Fibromyalgia

The recommended dose is 60 mg once daily. A lower starting dose of 30 mg may be considered for tolerability reasons in some patients, with a target dose of 60 mg/day within 1-2 weeks. Some patients may respond within the first week. There is no evidence that doses greater than 60 mg/day (e.g., 120 mg/day) confer additional benefit. Additionally, patients who do not respond to 60 mg/day may not respond to 120 mg/day (see 14 Clinical Trials). Furthermore, doses higher than 60 mg/day are associated with more severe and frequent rate of adverse reactions (see 8 Adverse Reactions). Daily doses above 120 mg have not been evaluated for safety or efficacy and are not recommended (see 14 Clinical Trials).

Chronic Low Back Pain

The recommended dose is 60 mg once daily. A lower starting dose of 30 mg may be considered for tolerability reasons in some patients, with a target dose of 60 mg/day within 1-2 weeks. Some patients may respond within the first week. There is no evidence that higher doses confer additional benefit, even in patients who do not respond to a 60 mg dose, and higher doses are associated with a higher rate of adverse reactions. Daily doses above 120 mg have not been evaluated for safety or efficacy and are not recommended (see 14 Clinical Trials).

All patients who participated in the chronic low back pain clinical trials had a clinical diagnosis of CLBP with pain present on most days for at least 6 months and no signs of radiculopathy or spinal stenosis (see 14 Clinical Trials).

Chronic Pain Associated with Osteoarthritis of the Knee

The recommended dose is 60 mg once daily. A lower starting dose of 30 mg may be considered for tolerability reasons in some patients, with a target dose of 60 mg/day within 1-2 weeks. Some patients may respond within the first week. Some patients may benefit from dosages above the recommended 60 mg once daily up to a maximum dose of 120 mg per day, although the higher dose has been associated with a higher rate of adverse reactions. Daily doses above 120 mg have not been evaluated for safety or efficacy and are not recommended (see 14 Clinical Trials).

Maintenance/Continuation/Extended Treatment

Major Depressive Disorder

It is generally agreed that acute episodes of major depression require several months or longer of sustained pharmacologic therapy beyond response to the acute episode. There is insufficient evidence available to answer the question of how long a patient should continue to be treated with AG-Duloxetine. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

Generalized Anxiety Disorder

During long-term therapy, the dosage should be maintained at the lowest effective level and patients should be periodically re-assessed to determine the need to continue treatment (see 14 Clinical Trials).

Fibromyalgia, Chronic Low Back Pain, Chronic Pain Associated with Osteoarthritis of the Knee, and Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

The efficacy of duloxetine delayed-release capsules beyond 12 weeks in DPN or FM and 13 weeks in CLBP or OA has not been evaluated in controlled clinical trials. The healthcare professional who elects to use AG-Duloxetine for extended periods in the treatment of FM, DPN, CLBP and OA should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

General Considerations for Dosing in Special Populations

- **Dosage for Elderly Patients (≥ 65 years of age):** For GAD, AG-Duloxetine should be initiated at a dose of 30 mg once daily for 2 weeks. For patients showing a response, 30 mg once daily may then be continued. For others, the dose can be increased to the target dose of 60 mg/day. In patients who continue to show insufficient response, patients may benefit from doses above 60 mg once daily. The maximum dose studied is 120 mg per day. For all other indications, no dose adjustment is recommended for elderly patients on the basis of age. Caution should be exercised in treating the elderly. Pharmacokinetic results suggest no overall differences between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. When individualizing the dosage, extra care should be taken when increasing the dose. (see 7.1.4 Geriatrics and 10.3 Pharmacokinetics: Special Populations and Conditions)
- **Pediatrics (<18 years of age):** The safety and efficacy of duloxetine delayed-release capsules in pediatric patients (<18 years of age) have not been established and its use in this patient population is not indicated (see 7 Warnings and Precautions: Psychiatric).
- **Dosage for Patients with Renal Impairment:** AG-Duloxetine is contraindicated in patients with end-stage renal disease (requiring dialysis) or in severe renal impairment (estimated creatinine clearance <30 mL/min) (see 2 Contraindications: Severe Renal Impairment, 7 Warnings and Precautions: Renal and 10 Clinical Pharmacology).
- **Dosage for Patients with Hepatic Impairment:** AG-Duloxetine is contraindicated in patients with any liver disease resulting in hepatic impairment (see 2 Contraindications: Hepatic Impairment, 7 Warnings and Precautions: Hepatic/Biliary/Pancreatic: Hepatic Impairment and 10 Clinical Pharmacology).
- **Treatment of Pregnant Women During the Third Trimester:** Post-marketing reports indicate that some neonates exposed to SSRIs or other newer antidepressants late in the third trimester have developed complications requiring prolonged hospitalization,

respiratory support, and tube feeding (see 7.1.1 Pregnancy). When treating pregnant women with AG-Duloxetine during the third trimester, the healthcare professional should carefully consider the potential risks and benefits of treatment. The healthcare professional may consider tapering AG-Duloxetine in the third trimester.

4.2.1 Discontinuing Treatment

When discontinuing AG-Duloxetine after more than 1 week of therapy, it is recommended that the dose be tapered to minimize the risk of discontinuation symptoms (see 7 Warnings and Precautions: Dependance, Tolerance and/or Abuse Liability: Discontinuation of Treatment and 8.1 Adverse Reaction Overview: Adverse Events Following Discontinuation of Treatment). 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 professional may continue decreasing the dose but at a more gradual rate.

4.4 Administration

AG-Duloxetine may be administered with or without food; however, food may help reduce the incidence of initial nausea. Results from a well-controlled dose comparison study (N=647) have demonstrated that patients taking duloxetine delayed-release capsules 60 mg/day with food experienced similar rates of nausea as patients treated with duloxetine delayed-release capsules 30 mg/day with or without food.

AG-Duloxetine should be swallowed whole and should not be chewed or crushed, nor should the contents be sprinkled on food or mixed with liquids. All of these might affect the enteric coating.

4.5 Missed Dose

In the event that a patient misses a dose, they should be instructed to take their dose as soon as they remember. If it is almost time for the next dose, the patient should skip the missed dose and take the next dose at the next scheduled time. The patient should not double the dose of AG-Duloxetine to make up for a missed dose.

5 Overdose

Human Experience: In clinical trials, cases of acute ingestions above 3000 mg, alone or in combination with other drugs, were reported, with none being fatal. However, in post marketing experience fatal outcomes have been reported for acute overdoses, primarily with mixed overdoses, but also with duloxetine only, at doses as low as approximately 1000 mg. Signs and symptoms of overdose (duloxetine alone or with mixed drugs) included somnolence, coma, serotonin syndrome, seizures, vomiting, and tachycardia.

Animal Experience: In animal studies, the major signs of overdose toxicity related to the central nervous and gastrointestinal systems. These included central nervous system effects such as tremors, clonic convulsions, ataxia, emesis, and decreased appetite.

Management of Overdose

No specific antidote is known, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. An airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal may be useful in limiting absorption. AG-Duloxetine has a large volume of distribution and forced diuresis, hemoperfusion, and exchange perfusion are unlikely to be beneficial.

In managing overdose, consider the possibility of multiple drug involvement. A specific caution involves patients who are taking or have recently taken duloxetine and might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and/or its active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see 9 Drug Interactions).

For the most recent information in the management of a suspected overdose, contact your regional Poison Control Centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 Dosage Forms, Strengths, Composition, and Packaging

Table 1: Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsule (delayed-release) / 30 mg and 60 mg	Ascorbic acid, hypromellose, hypromellose phthalate, sucrose, sugar spheres, talc and triethyl citrate. Cap and body: FD&C Blue No. 2, gelatin, iron oxide yellow (60 mg capsule only), sodium lauryl sulphate and titanium dioxide. Imprinting ink: Butyl alcohol, dehydrated alcohol, FD & C Blue No. 2 (30 mg capsule only), iron oxide yellow (30 mg capsule only), isopropyl alcohol, potassium hydroxide (60 mg capsule only), propylene glycol, purified

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
		water (60 mg capsule only), shellac, strong ammonia solution and titanium dioxide.

Description

Each capsule contains enteric-coated pellets of duloxetine hydrochloride equivalent to 30 mg or 60 mg of duloxetine that are designed to prevent degradation of the drug in the acidic environment of the stomach.

Duloxetine delayed-release capsules 30 mg: Opaque blue/opaque white hard gelatin capsules size “3” having imprinting “157” on body with green ink and “A” on cap with green ink filled with white to off-white colored pellets. Available in bottles of 30, 100, 500 & 1000 capsules and in cartons of 30 capsules (3 blister strips, 10 capsules per strip) & 100 capsules (10 blister strips, 10 capsules per strip)

Duloxetine delayed-release capsules 60 mg: Opaque blue/opaque green hard gelatin capsules size “1” having imprinting “158” on body with white ink and “A” on cap with white ink filled with white to off-white colored pellets. Available in bottles of 30, 100, 500 & 1000 and in cartons of 30 capsules (3 blister strips, 10 capsules per strip) & 100 capsules (10 blister strips, 10 capsules per strip)

Not all pack sizes and presentations may be marketed.

7 Warnings and Precautions

See 3 Serious Warnings and Precautions Box: Suicidal thoughts and behaviour.

See 9.1 Serious Drug Interactions: Monoamine Oxidase Inhibitors; Thioridazine; Potent CYP1A2 Inhibitors.

General

Concomitant Illness

Clinical experience with duloxetine delayed-release capsules in patients with concomitant systemic illnesses is limited. Caution is advisable when using AG-Duloxetine in patients with diseases or conditions that produce altered metabolism or hemodynamic responses. For example, caution should be exercised in using AG-Duloxetine in patients with conditions that slow gastric emptying (e.g., some patients with diabetic gastroparesis) (see 9.4 Drug-Drug Interactions: Potential for Interaction with Drugs that Affect Gastric Acidity).

Sucrose

AG-Duloxetine contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

Carcinogenesis and Genotoxicity

For animal data, (see 16 Non-Clinical: Toxicology) section.

Cardiovascular

Blood Pressure and Heart Rate

Duloxetine delayed-release capsules has been associated with an increase in blood pressure and clinically significant hypertension in some patients. This may be due to the noradrenergic effect of duloxetine.

In placebo-controlled clinical trials across all approved indications for change from baseline to endpoint, duloxetine delayed-release capsules treatment was associated with mean increases of 0.09 mm Hg in systolic and 0.65 mm Hg in diastolic blood pressure compared to mean decreases of 1.35 mm Hg systolic and 0.79 mm Hg diastolic in placebo-treated patients. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure (see 8.2 Clinical Trial Adverse Reactions: Vital Sign Changes). There was no significant difference between treatment groups in the rate of discontinuation due to elevated blood pressure.

Duloxetine delayed-release capsules treatment, for up to 26 weeks in placebo-controlled trials across all approved indications was associated with an increase in heart rate of 1.39 beats per minute (mean change from baseline to endpoint).

Cases of hypertensive crisis have been reported very rarely with duloxetine delayed-release capsules, especially in patients with pre-existing hypertension. AG-Duloxetine should be used with caution in patients with uncontrolled hypertension as it may expose them to hypertensive crisis (see 8.5 Post-Market Adverse Reactions).

Blood pressure and heart rate should be evaluated prior to initiating treatment and periodically measured throughout treatment, especially in patients with known hypertension and/or other cardiac disease. AG-Duloxetine should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure. Caution should also be exercised when AG-Duloxetine is used with drugs that may impair its metabolism (see 9 Drug Interactions). For patients who experience a sustained increase in blood pressure while receiving AG-Duloxetine either dose reduction or gradual discontinuation should be considered.

Electrocardiogram Changes

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

Electrocardiograms of 321 patients who received duloxetine delayed-release capsules in MDD placebo-controlled clinical trials and 728 patients who received duloxetine delayed-release capsules in DPN placebo-controlled clinical trials were evaluated; duloxetine delayed-release capsule was not associated with the development of clinically significant ECG abnormalities (see 8.4 Abnormal Laboratory Findings). Additionally, a clinical pharmacology study was conducted to assess the safety of duloxetine at the highest tolerable level of exposure of duloxetine (200 mg BID) and to measure QT interval. QT interval at doses up to 200 mg BID was not prolonged (see 10.2 Pharmacodynamics).

In MDD and DPN placebo-controlled clinical trials, duloxetine delayed-release capsules-treated patients did not develop abnormal ECGs at a rate different from that in placebo-treated patients (see 8.4 Abnormal Laboratory Findings).

Dependence, Tolerance and/or Abuse Liability

Dependence Liability

In animal studies, duloxetine did not demonstrate stimulant or barbiturate-like (depressant) abuse potential. Duloxetine did produce reductions in activity in rodents and monkeys. In drug dependence studies, duloxetine did not demonstrate any dependence-producing potential in monkeys or rats.

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

Discontinuation of Treatment

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

irritability, nightmare, insomnia, diarrhea, anxiety, hyperhidrosis, vertigo, somnolence, and myalgia.

Patients should be monitored for these symptoms when discontinuing treatment with AG-Duloxetine. 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, dose titration should be managed on the basis of the patient's clinical response (see 4.2 Recommended Dose and Dosage Adjustment: 4.2.1 Discontinuing Treatment and 8.1 Adverse Reaction Overview: Adverse Events Following Discontinuation of Treatment).

Driving and Operating Machinery

Any psychoactive drug may impair judgment, thinking, or motor skills. AG-Duloxetine may be associated with undesirable effects such as sedation and dizziness. Therefore, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that AG-Duloxetine therapy does not affect their ability to engage in such activities.

Endocrine and Metabolism

Glucose Regulation

In DPN trials, duloxetine delayed-release capsules treatment worsened glycemic control in some diabetic patients. In three clinical trials of duloxetine delayed-release capsules for the management of pain associated with DPN, the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 9.8 mmol/L (176 mg/dL), and the mean baseline hemoglobin A1c (HbA1c) was 7.8%. In the 12-week acute treatment phase of these studies, duloxetine delayed-release capsules were associated with a small increase in mean fasting blood glucose as compared to placebo. In the extension phase of these studies, which lasted up to 52 weeks, mean fasting blood glucose increased by 0.67 mmol/L (12 mg/dL) in the duloxetine delayed-release capsules group and decreased by 0.64 mmol/L (11.5 mg/dL) in the routine care group, which was statistically significantly different. HbA1c increased by 0.5% in the duloxetine delayed-release capsules group and by 0.2% in the routine care groups.

Hematologic

Abnormal Bleeding

SSRIs and SNRIs, including AG-Duloxetine, may increase the risk of bleeding events by causing abnormal platelet aggregation. Concomitant use of acetylsalicylic acid (ASA), nonsteroidal anti-inflammatory drugs (NSAIDS), warfarin and other anticoagulants may add to the risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of

gastrointestinal bleeding (see 8 Clinical Trial Adverse Reactions: Other Adverse Events – Gastrointestinal Bleeding, and 8.5 Post-Market Adverse Reactions). Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. An observational study showed an association between the occurrence of postpartum hemorrhage and exposure to duloxetine delayed-release capsules close to delivery (see 7.1.1 Pregnancy: Labour and/or Delivery).

Patients should be cautioned about the risk of bleeding associated with the concomitant use of AG-Duloxetine and NSAIDS, ASA, or other drugs that affect coagulation (see 9.4 Drug-Drug Interactions). Caution is advised in patients with a history of bleeding disorder or predisposing conditions (e.g. thrombocytopenia).

Hepatic/Biliary/Pancreatic

Hepatic Impairment

Patients with clinically evident hepatic impairment have decreased duloxetine metabolism and elimination. After a single non-therapeutic (20 mg) dose of duloxetine delayed-release capsules, 6 cirrhotic patients with moderate liver impairment (Child-Pugh Class B) had a mean plasma duloxetine clearance about 15% that of age- and gender-matched healthy subjects, with a 5-fold increase in mean exposure (AUC). Although C_{max} was similar to normals in the cirrhotic patients, the half-life was about 3 times longer. AG-Duloxetine is contraindicated in patients with any liver disease resulting in hepatic impairment (see 2 Contraindications: Hepatic Impairment; 4.2 Recommended Dose and Dosage Adjustment: General Considerations for Dosing in Special Populations and 10.3 Pharmacokinetics: Special Populations and Conditions).

Hepatotoxicity

Duloxetine delayed-release capsules increase the risk of elevation of serum aminotransferase levels. In clinical trials, the median time to detection of the aminotransferase elevation was about two months. In most patients, these were usually transient and self-limiting with continued use, or resolved upon discontinuation of duloxetine delayed-release capsules. Liver aminotransferase elevations resulted in the discontinuation of 0.3% (89/29,435) of duloxetine delayed-release capsules-treated patients.

In placebo-controlled trials in MDD, elevations of alanine aminotransferase (ALT) to >3 times the upper limit of normal occurred in 0.4% (8/1902) of duloxetine delayed-release capsules-treated patients and in 0.2% (2/1200) of placebo-treated patients. In placebo-controlled trials in DPN, elevations of ALT to >3 times the upper limit of normal occurred in 2% (13/662) of duloxetine delayed-release capsules-treated patients and in 0% (0/281) of placebo-treated patients.

In the full cohort of placebo-controlled trials in any indication for patients with normal and abnormal baseline ALT values, elevation of ALT >3 times the upper limit of normal occurred in 1.37% (132/9611) of duloxetine delayed-release capsules-treated patients compared with 0.49% (35/7182) of placebo-treated patients. In placebo-controlled studies using a fixed-dose design, there was evidence of a dose-response relationship for ALT and AST elevation of >3 times the upper limit of normal and >5 times the upper limit of normal, respectively.

Postmarketing reports have described cases of hepatitis with abdominal pain, hepatomegaly and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported (see 8.5 Post-Market Adverse Reactions: Hepatic).

The combination of aminotransferase elevations and elevated bilirubin, without evidence of cholestasis, is generally recognized as an important predictor of severe liver injury. In clinical trials, 7 duloxetine delayed-release capsules patients had elevations of aminotransferase and bilirubin, but 5 of 7 also had elevation of alkaline phosphatase, suggesting an obstructive process; in 3 of these 7 patients, there was evidence of heavy alcohol use and this may have contributed to the abnormalities seen. Two placebo-treated patients also had aminotransferase elevations with elevated bilirubin.

Post-marketing reports indicate that elevated aminotransferase, bilirubin, and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis. Severe elevations of liver enzymes (>10 times the upper limit of normal) or liver injury with a cholestatic or mixed pattern have been rarely reported, in some cases associated with excessive alcohol use or pre-existing liver disease. Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, AG-Duloxetine should ordinarily not be prescribed to patients with substantial alcohol use (see 7 Warnings and Precautions: Hepatic/Biliary/Pancreatic: Use in Patients with Substantial Alcohol Use). AG-Duloxetine should not be used in patients with any liver disease resulting in hepatic impairment (see 2 Contraindications: Hepatic Impairment). AG-Duloxetine should be used with caution in patients treated with other drugs associated with hepatic injury (see 8.5 Post-Market Adverse Reactions: Hepatic).

Severe hepatic injury, associated with jaundice, has been reported very rarely in patients with non-alcoholic fatty liver disease (NAFLD). It is not clear whether these events are related to use of duloxetine or to other factors.

Healthcare professionals should be aware of the signs and symptoms of liver damage (e.g. pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained "flu-like" symptoms) and should investigate such symptoms promptly. AG-Duloxetine should be discontinued and should not be restarted in patients with jaundice.

Use In Patients with Substantial Alcohol Use

Use of AG-Duloxetine in patients who consume substantial amounts of alcohol may be associated with severe liver injury. Isolated cases of liver failure, including fatal cases, have been reported. AG-Duloxetine should only be used in exceptional circumstances and with extreme caution in these patients (see 8.5 Post-Market Adverse Reactions: Hepatic).

Musculoskeletal

Bone Fracture Risk

Epidemiological studies show an increased risk of bone fractures following exposure to some antidepressants, including SSRIs/SNRIs. The risks appear to be greater at the initial stages of treatment, but significant increased risks were also observed at later stages of treatment. The possibility of fracture should be considered in the care of patients treated with AG-Duloxetine. Elderly patients and patients with important risk factors for bone fractures should be advised of possible adverse events which increase the risk of falls, such as dizziness and orthostatic hypotension, especially at the early stages of treatment but also soon after withdrawal. Preliminary data from observational studies show association of SSRIs/SNRIs and low bone mineral density in older men and women. Until further information becomes available, a possible effect on bone mineral density with long term treatment with SSRIs/SNRIs, including AG-Duloxetine, cannot be excluded, and may be a potential concern for patients with osteoporosis or major risk factors for bone fractures.

Neurologic

Seizures

Although anticonvulsant effects of duloxetine have been observed in animal studies, duloxetine delayed-release capsules have not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarketing testing. In placebo-controlled clinical trials across all indications, seizures/convulsions occurred in 0.03% (3/10,524) of patients treated with duloxetine and 0.01% (1/7699) of patients treated with placebo. As with other CNS active drugs, AG-Duloxetine should be used with caution in patients with a history of a seizure disorder.

Serotonin Syndrome/Neuroleptic Malignant Syndrome

On rare occasions serotonin syndrome or neuroleptic malignant syndrome-like events have occurred in association with treatment with SSRIs, particularly when given in combination with other serotonergic and/or neuroleptic drugs. Serotonin syndrome symptoms may include mental status changes (e.g., confusion, irritability, extreme agitation progressing to delirium and coma), autonomic instability with rapid fluctuations of vital signs (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., rigidity, myoclonus, hyperreflexia,

incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). As these syndromes may result in potentially life-threatening conditions, treatment with AG-Duloxetine should be discontinued if such events occur and supportive symptomatic treatment should be initiated. AG-Duloxetine should not be used in combination with MAOIs, including the antibiotic linezolid and the thiazine dye methylthioninium chloride (methylene blue) which are less well-known examples of MAOIs,) or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome (see 2 Contraindications and 9 Drug Interactions).

Triptans (5HT1 Agonists)

Cases of life-threatening serotonin syndrome have been reported during combined use of selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans. If concomitant treatment with AG-Duloxetine and a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. (See 7 Warnings and Precautions: Neurologic: Serotonin Syndrome/Neuroleptic Malignant Syndrome, and 9.4 Drug-Drug Interactions: Triptans ($5HT_1$ agonists).

Ophthalmologic

Angle-Closure Glaucoma

As with other antidepressants, AG-Duloxetine can cause mydriasis, which may trigger an angle-closure attack in a patient with anatomically narrow ocular angles. Healthcare providers should inform patients to seek immediate medical assistance if they experience eye pain, changes in vision or swelling or redness in or around the eye.

Psychiatric

Potential Association with Behavioural and Emotional Changes, Including Self-Harm

Pediatrics: Placebo-Controlled Clinical Trial Data

- Recent analyses of placebo-controlled clinical trial safety databases from selective serotonin reuptake inhibitors (SSRIs) and other newer antidepressants suggest that use of these drugs in patients under the age of 18 may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo.
- The small denominators in the clinical trials database, as well as the variability in placebo rates, preclude reliable conclusions on the relative safety profiles among these drugs.

Adults and Pediatrics: Additional data

- There are clinical trial and post-marketing reports with SSRIs and other newer antidepressants, in both pediatrics and adults, of severe agitation-type adverse events coupled with self-harm or harm to others. The agitation-type events include: akathisia, agitation, disinhibition, emotional lability, hostility, aggression, and depersonalization. In some cases, the events occurred within several weeks of starting treatment.

Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioural changes.

An FDA meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients ages 18 to 24 years with psychiatric disorder showed an increased risk of suicidal behaviour with antidepressants compared to placebo.

Suicide

The possibility of a suicide attempt is inherent in MDD and other psychiatric disorders and may persist until significant remission occurs. As with other drugs with similar pharmacological action (inhibitor of serotonin reuptake [SSRI] or inhibitor of serotonin and norepinephrine reuptake [SNRI]), isolated cases of suicidal ideation and suicidal behaviours have been reported during duloxetine delayed-release capsules therapy or early after treatment discontinuation.

Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose (see 4.2 Recommended Dose and Dosage Adjustment: 4.2.1 Discontinuing Treatment, 7 Warnings and Precautions: Psychiatric, and 8.1 Adverse Reaction Overview: Adverse Events Following Discontinuation of Treatment).

Because of the well established comorbidity between depression and other psychiatric disorders, the same precautions observed when treating patients with depression should be observed when treating patients with other psychiatric disorders (see 7 Warnings and Precautions: Psychiatric).

Healthcare professionals should encourage patients to report any distressing thoughts or feelings at any time.

Activation of Mania/Hypomania In placebo-controlled trials in patients with MDD, activation of mania or hypomania was reported in 0.1% (2/2489) of duloxetine delayed-release capsules-treated patients and 0.1% (1/1625) of placebo-treated patients. No activation of mania or hypomania was reported in GAD, DPN, FM, CLBP or OA placebo-controlled trials. Activation of mania/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 MDD. As with similar CNS active drugs, AG-Duloxetine should be used cautiously in patients with a history of mania.

A major depressive episode may be the initial presentation of bipolar disorder. Patients with bipolar disorder may be at an increased risk of experiencing manic episodes when treated with antidepressants alone. Therefore, the decision to initiate symptomatic treatment of depression should be made only after patients have been adequately assessed to determine if they are at risk for bipolar disorder.

Akathisia/Psychomotor Restlessness

The use of SSRI's and other newer antidepressants, including duloxetine, has been very rarely associated with the development of akathisia, which is characterized by a subjectively unpleasant or distressing restlessness and a need to move, often accompanied by an inability to sit or stand. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Renal

Increased plasma concentrations of duloxetine occur in patients with end-stage renal disease (requiring dialysis). For this reason AG-Duloxetine is not recommended for patients with end-stage renal disease or severe renal impairment (see 2 Contraindications: Severe Renal Impairment; 4.2 Recommended Dose and Dosage Adjustment: General Consideration for Dosing in Special Populations and 10.3 Pharmacokinetics: Special Populations and Conditions, Renal Insufficiency).

Urinary Hesitation and Retention

AG-Duloxetine is in a class of drugs known to affect urethral resistance. Urinary hesitation and retention have been observed in clinical trials for various indications. Spontaneous post-marketing cases of urinary hesitation and retention have been reported. In some instances of urinary retention associated with duloxetine delayed-release capsules therapy, hospitalization and/or catheterization was required. If symptoms of urinary hesitation develop during treatment with AG-Duloxetine, discontinuation or dose-reduction should be considered. Caution should also be exercised in prescribing AG-Duloxetine to patients who use concomitant medications that may affect voiding (e.g., anticholinergics; see 8.2 Clinical Trial Adverse Reactions: Other Adverse Events).

Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including AG-Duloxetine. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported and appeared to be reversible when duloxetine delayed-release capsules were discontinued. Elderly patients may be at greater risk of developing hyponatremia

with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk. Discontinuation of AG-Duloxetine should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. More severe and/or acute cases have been associated with hallucination, syncope, seizure, coma, respiratory arrest, and death (see 8.5 Post-Market Adverse Reactions).

Reproductive Health

- **Function**

  Serotonin-norepinephrine reuptake inhibitors may cause symptoms of sexual dysfunction (see 8.2 Clinical Trial Adverse Reactions, Sexual Dysfunction). Patients should be informed that there have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SNRIs.

Skin

Serious Dermatological Reactions

There have been very rare post-marketing reports of serious cutaneous reactions including Stevens-Johnson Syndrome (SJS) and erythema multiforme in patients treated with duloxetine delayed-release capsules (see 8.5 Post-Market Adverse Reactions). Post-market reporting rate is generally accepted to be an underestimate due to under-reporting. In some cases, causality in relation to duloxetine delayed-release capsules could not be established. Patients should be advised that if they experience a skin rash, they should discontinue AG-Duloxetine treatment and contact their healthcare professional for assessment and advice.

7.1 Special Populations

7.1.1 Pregnancy

Safe use of duloxetine delayed-release capsules during pregnancy has not been established. Therefore, AG-Duloxetine should not be administered to pregnant women or those intending to become pregnant, unless, in the opinion of the treating healthcare professional, the expected benefits to the patient markedly outweigh the possible hazards to the fetus.

There are no adequate and well-controlled studies in pregnant women. In animal reproductive studies, duloxetine and/or its metabolites were found to cross the placenta in rats and duloxetine has been shown to have adverse effects on embryo/fetal and post-natal development (see 16 Non-Clinical Toxicology). Because animal reproduction studies are not always predictive of human response and because of the possibility that duloxetine and/or its

metabolites may have adverse effects on the newborn, the use of this drug during pregnancy should only be considered if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Post-marketing reports indicate that some neonates exposed to SSRIs or newer antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and other newer antidepressants or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see 2 Contraindications: MAOIs). When treating a pregnant woman with AG-Duloxetine during the third trimester, the healthcare professional should carefully consider the potential risks and benefits of treatment (see 4.2 Recommended Dose and Dosage Adjustment: General Considerations for Dosing in Special Populations: Treatment of Pregnant Women During the Third Trimester).

Patients should be advised to notify their healthcare professional if they become pregnant or intend to become pregnant during therapy.

Labour and/or Delivery

An observational study evaluating the risks of maternal outcomes associated with exposure to duloxetine during pregnancy demonstrated an increased risk of postpartum hemorrhage for women exposed to duloxetine. The risk of postpartum hemorrhage was 36/1000 (95% confidence interval 24.8-49.4) women exposed to duloxetine close to delivery (final 30 days of pregnancy) compared to 23/1000 (95% confidence interval 23.1-23.4) women who were not exposed to duloxetine during pregnancy [adjusted relative risk 1.53 (95% confidence interval 1.08-2.18)].

In observational study data, maternal exposure to duloxetine during pregnancy was associated with an increased risk for preterm birth (less than 2-fold). The majority of the premature births occurred between 35 and 36 weeks of gestation.

When treating a pregnant woman the use of duloxetine should only be considered if the potential benefit justifies the potential risk to the fetus.

7.1.2 Breastfeeding

Duloxetine is excreted into the milk of lactating women. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose. Because the safety of duloxetine in infants is not known, nursing while on AG-Duloxetine is not recommended.

Patients should be advised to notify their healthcare professional if they are breastfeeding.

7.1.3 Pediatrics

Pediatrics (<18 years of age)

The safety and efficacy of duloxetine delayed-release capsules in pediatric patients (<18 years of age) have not been established and Health Canada has not authorized an indication for pediatric use. (See 3 Serious Warnings and Precautions Box and 7 Warnings and Precautions: Psychiatric).

7.1.4 Geriatrics

Geriatrics (≥65 years of age)

Of the 2418 duloxetine delayed-release capsules-treated patients in the MDD clinical studies 5.9% (143) were 65 years of age or over. Of the 1169 duloxetine delayed-release capsules-treated patients in the acute placebo-controlled GAD studies, 17.2% (201) were 65 years of age or over. Of the 1429 duloxetine delayed-release capsules-treated patients in the DPN studies, 31.9% (456) were 65 years of age or over. Of the 1226 duloxetine delayed-release capsules-treated patients in FM studies, 7.9% (97) were 65 years of age or over. Of the 600 duloxetine delayed-release capsules-treated patients in CLBP placebo-controlled clinical studies, 22.3% (134) were 65 years of age or over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and although other reported clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out (see 7 Warnings and Precautions: Musculoskeletal: Bone Fracture Risk; 7 Warnings and Precautions: Renal: Hyponatremia).

8 Adverse Reactions

8.1 Adverse Reaction Overview

Major Depressive Disorder (MDD)

Duloxetine delayed-release capsules has been evaluated for safety in 2418 patients diagnosed with MDD who participated in multiple-dose pre-marketing trials, representing 1099 patient-years of exposure. Among these 2418 duloxetine delayed-release capsules-treated patients, 1139 patients participated in eight 8- or 9-week, placebo-controlled trials at doses ranging from 40 to 120 mg/day, while the remaining 1279 patients were followed for up to 1-year in an open-label safety study using flexible doses between 80 and 120 mg/day. Two placebo-controlled

studies with doses of 80 and 120 mg/day had 6-month maintenance extensions. Of these 2418 patients, 993 duloxetine delayed-release capsules-treated patients were exposed for at least 180 days and 445 duloxetine delayed-release capsules-treated patients were exposed for at least 1 year. The long-term safety of duloxetine delayed-release capsules in MDD patients has also been evaluated in 533 patients in one long-term maintenance of effect study consisting of a 12-week, open-label, acute phase followed by a 26-week, double-blind continuation phase and in 514 patients in another long-term maintenance of effect study consisting of a 4 to 10 week, open-label, acute phase, a 24-week, open-label, continuation phase followed by a 52-week, double-blind, maintenance phase.

Generalized Anxiety Disorder (GAD)

Duloxetine delayed-release capsules have also been evaluated for safety in 1797 patients with GAD. Most patients in the acute placebo-controlled studies received duloxetine delayed-release capsules 60 mg QD or 120 mg QD as their final dose.

Neuropathic Pain Associated with Diabetic Peripheral Neuropathy (DPN)

Duloxetine delayed-release capsules have also been evaluated for safety in 1429 patients with neuropathic pain associated with DPN representing 894.13 patient-years of exposure. Among these 1429 duloxetine delayed-release capsules-treated patients, 800 patients participated in three 12- to 13-week, placebo-controlled trials at doses ranging from 20 to 120 mg/day. An additional 449 patients were enrolled in an open-label safety study using 120 mg/day for a duration of 6 months (87 patients continued on to an open-label extension phase for an additional 24 weeks). Another 57 patients, originally treated with placebo, were exposed to duloxetine delayed-release capsules for up to 12 months at 60 mg twice daily in an extension phase. Among these 1429 patients, 881 had ≥6 months of exposure to duloxetine delayed-release capsules, and 515 had greater than 12 months of exposure.

Fibromyalgia

Duloxetine delayed-release capsules have also been evaluated for safety in 1236 patients with fibromyalgia. In placebo-controlled trials, 369 patients received duloxetine delayed-release capsules 60 mg QD (120.08 patient-years), 221 patients received duloxetine delayed-release capsules 120 mg QD (102.18 patient-years), and 220 patients received duloxetine delayed-release capsules 60 mg BID (36.49 patient-years) as a maximum dose.

Chronic Low Back Pain

Duloxetine delayed-release capsules have been evaluated for safety in 698 patients with CLBP (representing 237.99 patient-years exposure to duloxetine). In 12- to 13-week placebo-controlled studies, the majority of the duloxetine delayed-release capsules-treated patients (428, 71.3%) received duloxetine delayed-release capsules 60 mg QD. Approximately a quarter of duloxetine delayed-release capsules-treated patients (139, 23.2%) received duloxetine 120 mg QD at some point during the acute phase.

Chronic Pain Associated with Osteoarthritis (OA) of the Knee

Duloxetine delayed-release capsules have been evaluated for safety in 503 duloxetine-treated patients with OA of the knee in two 13-week, placebo-controlled trials and one 10-week placebo-controlled "add-on" trial with NSAIDs (see 14 Clinical Trials).

Commonly Observed Adverse Events

In clinical trials, the most commonly observed adverse events associated with the use of duloxetine delayed-release capsules and not seen at an equivalent incidence among placebo treated patients were: abdominal pain, back pain, constipation, decreased appetite, diarrhea, dizziness, dry mouth, erectile dysfunction, fatigue, headache, hyperhidrosis, increased sweating, insomnia, nasopharyngitis, nausea, somnolence, and vomiting.

Adverse Events Reported as Reasons for Discontinuation of Treatment

Placebo-Controlled MDD Trials: Approximately 10% of the 1139 patients who received duloxetine delayed-release capsules in acute placebo-controlled trials discontinued treatment due to an adverse event, compared with 4% of the 777 patients receiving placebo. Nausea (duloxetine delayed-release capsules 1.4%, placebo 0.1%) was the only common adverse event reported as 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).

Placebo-Controlled GAD Trials: Approximately 14% of the 910 patients who received duloxetine delayed-release capsules in acute placebo-controlled trials for GAD discontinued treatment due to an adverse event, compared with 5.3% of the 665 patients receiving placebo. Nausea (duloxetine delayed-release capsules 3.3%, placebo 0.5%) and dizziness (duloxetine delayed-release capsules 1.0%, placebo 0.5%) were the common adverse events reported as reasons for discontinuation and considered to be drug-related (as defined under MDD Trials, above).

Placebo-Controlled Trials for Neuropathic Pain Associated with DPN: Approximately 12% of the 800 patients who received duloxetine delayed-release capsules in acute placebo-controlled trials discontinued treatment due to an adverse event, compared with 5% of the 339 patients receiving placebo. Nausea (duloxetine delayed-release capsules 3.0%, placebo 0.3%), dizziness (duloxetine delayed-release capsules 1.1%, placebo 0.3%), and somnolence (duloxetine delayed-release capsules 1.2%, placebo 0%) were the common adverse events reported as reasons for discontinuation and considered to be drug-related (as defined under MDD Trials, above).

Placebo-Controlled FM Trials: Approximately 19% of the 876 patients who received duloxetine delayed-release capsules in placebo-controlled trials for FM discontinued treatment due to an adverse event, compared with 11.8% of the 535 patients receiving placebo. Nausea (duloxetine delayed-release capsules 1.9%, placebo 0.7%), fatigue (duloxetine delayed-release capsules 1.3%, placebo 0.2%) and somnolence (duloxetine delayed-release capsules 1.5%, placebo 0%) were the common adverse events reported as reasons for discontinuation and considered to be drug-related (as defined under MDD Trials, above).

Placebo-Controlled CLBP Trials: Approximately 17% of the 600 patients who received duloxetine delayed-release capsules in 13-week placebo-controlled trials for CLBP discontinued treatment due to an adverse reaction, compared with 6.3% of the 441 patients receiving placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine delayed-release capsules 3.0%, placebo 0.7%) and somnolence (duloxetine delayed-release capsules 1.0%, placebo 0.0%).

Placebo-Controlled OA Trials: Approximately 16% of the 239 patients who received duloxetine delayed-release capsules in 13 week placebo-controlled trials for chronic pain due to OA of the knee discontinued treatment due to an adverse reaction, compared with 5.6% of the 248 patients receiving placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine delayed-release capsules 2.9%, placebo 0.8%) and asthenia (duloxetine delayed-release capsules 1.3%, placebo 0.0%). Similarly, more patients taking duloxetine delayed-release capsules (40/264, or 15.2%) discontinued from the 10 week placebo-controlled, “add-on” trial with NSAIDs due to adverse events than did patients in the placebo group (23/260, or 8.8%).

Adverse Events Following Discontinuation of Treatment

Discontinuation symptoms have been systematically evaluated in patients taking duloxetine delayed-release capsules. Following abrupt or tapered discontinuation in placebo-controlled clinical trials, the following symptoms occurred at a rate greater than or equal to 1% and at a significantly higher rate in duloxetine delayed-release capsules-treated patients compared with those discontinuing from placebo: dizziness, nausea, headache, paresthesia, fatigue, vomiting, irritability, nightmare, insomnia, diarrhea, anxiety, hyperhidrosis, vertigo, somnolence, and myalgia. Although these events are generally self-limiting, some have been reported to be severe. (see 4.2 Recommended Dose and Dosage Adjustment: 4.2.1 Discontinuing Treatment and 7 Warnings and Precautions: Dependence, Tolerance and/or Abuse Liability: Discontinuation of Treatment).

8.2 Clinical Trial Adverse Reactions

The data in the following tables and text cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with data obtained from other clinical investigations involving different treatments,

uses, or investigators. The cited data provide the prescribing healthcare professional with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence in the population studied.

Adverse Events Occurring Among Duloxetine Delayed-Release Capsules -Treated Patients in Placebo-Controlled Major Depressive Disorder (MDD) Trials

Table 2 lists the incidence of treatment-emergent adverse events that occurred in 2% or more of patients treated with duloxetine delayed-release capsules in the acute phase of MDD placebo-controlled trials and with an incidence greater than placebo. The most commonly observed adverse events in duloxetine delayed-release capsules-treated MDD patients (incidence 5% or greater and at least twice the incidence in placebo patients) were: nausea, dry mouth, constipation, decreased appetite, fatigue, somnolence, and increased sweating. MedDRA terminology has been used to classify reported adverse events.

Table 2: Treatment-Emergent Adverse Events Incidence in the Acute Phase of MDD Placebo-Controlled Trials[1]

System Organ Class/Adverse Event	Percentage of Patients Reporting Event	
	Placebo (N = 777)	Duloxetine Delayed-Release Capsules (N = 1139)
Gastrointestinal Disorders		
Nausea	7	20
Dry mouth	6	15
Constipation	4	11
Diarrhea	6	8
Vomiting	3	5
Metabolism and Nutrition Disorders		
Appetite decreased [2]	2	8
General Disorders		
Fatigue	4	8
Investigations		
Weight decreased	1	2
Nervous System Disorders		

System Organ Class/Adverse Event	Percentage of Patients Reporting Event	
	Placebo (N = 777)	Duloxetine Delayed-Release Capsules (N = 1139)
Dizziness	5	9
Somnolence	3	7
Tremor	1	3
Skin and Subcutaneous Tissue Disorders		
Sweating increased	2	6
Vascular Disorders		
Hot flushes	1	2
Eye Disorders		
Vision blurred	1	4
Psychiatric Disorders		
Anxiety	2	3
Insomnia [3]	6	11
Libido decreased	1	3
Anorgasmia	1	3
Reproductive System		
Erectile dysfunction [4,5]	1	4
Ejaculation delayed [4]	1	3
Ejaculation dysfunction [4,5]	1	3

[1] Events reported by at least 2% of patients treated with duloxetine delayed-release capsules and more often than with placebo. The following events were reported by at least 2% of patients treated with duloxetine delayed-release capsules for MDD and had an incidence equal to or less than placebo: upper abdominal pain, palpitations, dyspepsia, back pain, arthralgia, headache, pharyngitis, cough, nasopharyngitis, and upper respiratory tract infection.

[2] Term includes anorexia

[3] Term includes middle insomnia

[4] Male patients only

[5] Term includes ejaculation disorder and ejaculation failure

Adverse events seen in men and women were generally similar except for effects on sexual function (see 8.2 Clinical Trial Adverse Reactions: Sexual Dysfunction). Clinical studies of duloxetine delayed-release capsules did not suggest a difference in adverse event rates in people over or under 65 years of age. There were too few non-Caucasian patients studied to determine if these patients responded differently from Caucasian patients.

Table 3 lists the incidence of treatment-emergent adverse events that occurred in 2% or more of patients treated with duloxetine delayed-release capsules in a long-term maintenance of effect study in MDD patients. The most commonly observed adverse events in duloxetine delayed-release capsules-treated MDD patients (incidence 5% or greater) during the double-blind maintenance phase included back pain, headache, nasopharyngitis, and fatigue.

Table 3: Treatment-Emergent Adverse Events Incidence from a Long-term Maintenance of MDD Effect Study

System Organ Class/ Adverse Events	Percentage of Patients Reporting Event			
	Acute Phase	Continuation Phase	Maintenance Phase	
	Duloxetine Delayed-Release Capsules (N=514)	Duloxetine Delayed-Release Capsules (N=413)	Placebo (N=142)	Duloxetine Delayed-Release Capsules (N=146)
Cardiac Disorders				
Palpitations	1	<1	1	3
Angina Pectoris	0	0	<1	2
Ear and Labyrinth Disorders				
Vertigo	3	1	3	0
Gastrointestinal Disorders				
Nausea	29	1	5	4
Dry mouth	15	3	<1	3
Constipation	9	3	0	0
Diarrhoea	7	4	3	1
Vomiting	5	1	1	1
Abdominal pain upper	3	2	1	3

System Organ Class/ Adverse Events	Percentage of Patients Reporting Event			
	Acute Phase	Continuation Phase	Maintenance Phase	
	Duloxetine Delayed-Release Capsules (N=514)	Duloxetine Delayed-Release Capsules (N=413)	Placebo (N=142)	Duloxetine Delayed-Release Capsules (N=146)
Abdominal pain	2	1	1	2
Dyspepsia	1	1	2	3
General Disorders and Administration Site Conditions				
Fatigue	12	2	3	6
Edema peripheral	<1	<1	2	2
Immune System Disorders				
Hypersensitivity	<1	<1	0	2
Infections and Infestations				
Nasopharyngitis	3	6	8	6
Influenza	1	3	8	3
Bronchitis	<1	2	3	3
Investigations				
Weight increased	<1	2	0	2
Metabolism and Nutrition Disorders				
Decreased appetite	5	<1	0	0
Anorexia	4	0	<1	<1
Diabetes Mellitus	0	<1	<1	2
Musculoskeletal and Connective Tissue Disorders				
Back pain	2	5	5	9
Arthralgia	<1	2	<1	4
Musculoskeletal pain	<1	2	<1	2
Pain in extremity	<1	1	2	3
Nervous System Disorders				
Headache	15	9	8	9
Dizziness	8	2	6	3

System Organ Class/ Adverse Events	Percentage of Patients Reporting Event			
	Acute Phase	Continuation Phase	Maintenance Phase	
	Duloxetine Delayed-Release Capsules (N=514)	Duloxetine Delayed-Release Capsules (N=413)	Placebo (N=142)	Duloxetine Delayed-Release Capsules (N=146)
Tremor	4	0	0	0
Somnolence	3	<1	0	0
Cervicobrachial syndrome	0	<1	0	2
Psychiatric Disorders				
Insomnia	5	3	6	5
Libido decreased	3	1	<1	0
Restlessness	3	<1	1	<1
Depression	<1	<1	1	2
Renal and Urinary Disorders				
Pollakiuria	2	<1	1	0
Skin and Subcutaneous Tissue Disorders				
Hyperhidrosis	15	6	1	5

Adverse Events Occurring Among Duloxetine Delayed-Release Capsules-Treated Patients in Placebo-Controlled Generalized Anxiety Disorder (GAD) Trials

Table 4 lists the incidence of treatment-emergent adverse events that occurred in ≥2% of patients treated with duloxetine delayed-release capsules in the GAD acute placebo-controlled trials and with an incidence greater than placebo. The most commonly observed adverse events in duloxetine delayed-release capsules-treated GAD patients (incidence 5% or greater and at least twice the incidence in placebo patients) included nausea, dizziness, dry mouth, fatigue, constipation, somnolence and increased sweating.

Table 4: Treatment-Emergent Adverse Events Incidence in the Acute Phase of GAD Placebo-Controlled Trials[1]

System Organ Class/Adverse Event	Percentage of Patients Reporting Event	
	Placebo (N = 665)	Duloxetine Delayed-Release Capsules (N = 910)
Gastrointestinal Disorders		
Nausea	10	34
Dry mouth	4	12
Constipation	4	10
Diarrhea	6	8
Vomiting	3	5
Metabolism and Nutrition Disorders		
Appetite decreased[2]	1	4
General Disorders		
Fatigue	4	11
Investigations		
Weight decreased	1	4
Nervous System Disorders		
Dizziness	8	14
Somnolence	2	8
Tremor	1	4
Skin and Subcutaneous Tissue Disorders		
Sweating increased	2	7
Vascular Disorders		
Hot flushes	1	2
Eye Disorders		
Vision blurred	1	4
Psychiatric Disorders		
Anxiety	1	2

System Organ Class/Adverse Event	Percentage of Patients Reporting Event	
	Placebo (N = 665)	Duloxetine Delayed-Release Capsules (N = 910)
Insomnia[3]	4	8
Libido decreased	1	5
Respiratory, Thoracic and Mediastinal Disorder		
Yawning	0	3
Reproductive System		
Erectile dysfunction[4,5]	0	2

[1] Events reported by at least 2% of patients treated with duloxetine delayed-release capsules and more often than with placebo.

[2] Term includes anorexia

[3] Term includes middle insomnia

[4] Male patients only

[5] Term includes ejaculation disorder and ejaculation failure

Dose Dependency of Adverse Events in GAD

Adverse events that occurred in the duloxetine 120 mg/day group at an incidence rate that was 5% or greater, and approximately twice that of the duloxetine 60 mg/day group included the following: increased sweating (15.3% versus 8.3%), diarrhea (7.6% versus 3.0%), and vomiting (6.5% versus 3.0%).

Adverse Events Occurring Among Duloxetine Delayed-Release Capsules-Treated Patients in Placebo-Controlled Trials of Pain Associated with Diabetic Peripheral Neuropathy (DPN):

Table 5 lists the incidence of treatment-emergent adverse events that occurred in 2% or more of patients treated with duloxetine delayed-release capsules in the acute phase (12-week) of DPN placebo-controlled trials (doses of 20 to 120 mg/day) and with an incidence greater than placebo. The most commonly observed adverse events in duloxetine delayed-release capsules-treated DPN patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were: nausea, constipation, dry mouth, vomiting, fatigue, decreased appetite, somnolence, erectile dysfunction, and hyperhidrosis. MedDRA terminology has been used to classify reported adverse events.

Table 5: Treatment-Emergent Adverse Events Incidence in the Acute Phase of Neuropathic Pain Associated with DPN Placebo-Controlled Trials[1]

System Organ Class/ Adverse Event	Percentage of Patients Reporting Event			
	Duloxetine Delayed-Release Capsules 60 QD N=344	Duloxetine Delayed-Release Capsules 60 BID N=341	Duloxetine Delayed-Release Capsules Total* N=800	PLACEBO N=339
Gastrointestinal Disorders				
Nausea	24	27	24	9
Diarrhea	11	7	10	7
Constipation	8	12	9	2
Dry mouth	6	10	8	3
Vomiting	5	6	6	3
Dyspepsia[2]	4	4	4	2
General Disorders and Administration Site Conditions				
Fatigue[3]	12	16	12	6
Abdominal Pain[4]	5	2	4	2
Infections and Infestations				
Nasopharyngitis	5	7	6	5
Influenza[5]	3	2	3	3
Metabolism and Nutrition Disorders				
Decreased appetite[6]	7	14	10	1
Musculoskeletal and Connective Tissue Disorders				
Back pain	5	2	4	3
Muscle spasm	3	3	3	2
Nervous System Disorder				
Somnolence[7]	17	21	17	5
Headache	12	11	12	9
Dizziness	11	13	11	6
Paresthesia[8]	2	2	2	1

System Organ Class/ Adverse Event	Percentage of Patients Reporting Event			
	Duloxetine Delayed-Release Capsules 60 QD N=344	Duloxetine Delayed-Release Capsules 60 BID N=341	Duloxetine Delayed-Release Capsules Total* N=800	PLACEBO N=339
Psychiatric Disorders				
Insomnia[9]	8	10	9	5
Agitation[10]	3	3	3	1
Renal and Urinary Disorders				
Pollakiuria	1	3	2	1
Reproductive System and Breast Disorder				
Erectile dysfunction[11]	2	8	5	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough[12]	3	4	4	4
Pharyngolaryngeal pain	1	4	3	2
Skin and Subcutaneous Tissue Disorders				
Sweating increased	8	10	9	2

* Includes all doses used in DPN studies (i.e. 20mg QD, 60mg QD and 60mg BID)

1 Events reported by at least 2% of patients treated with duloxetine delayed-release capsules and more often than placebo. The following events were reported by at least 2% of patients treated with duloxetine delayed-release capsules for DPNP and had an incidence equal to or less than placebo: pain in extremity, upper respiratory tract infection, arthralgia, cough, influenza, pruritus, musculoskeletal pain (includes myalgia and neck pain), and edema peripheral.

2 Includes stomach discomfort.

3 Also includes asthenia.

4 Includes abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort, and gastrointestinal pain.

5 2.8% of patients treated with duloxetine delayed-release capsules; 2.7% of patients who received placebo.

6 Includes anorexia.

7 Includes hypersomnia, sedation.

[8] Includes hypoesthesia, hypoesthesia facial, and paresthesia oral.

[9] Also includes middle insomnia, early morning awakening, and initial insomnia.

[10] Also includes feeling jittery, nervousness, restlessness, tension, and psychomotor agitation.

[11] Male patients only. (Duloxetine delayed-release capsules 60 mg QD, N=201; duloxetine delayed-release capsules 60 mg BID, N=190; all duloxetine delayed-release capsules, N=466; placebo, N=181).

[12] 3.9% of patients treated with duloxetine delayed-release capsules; 3.8% of patients who received placebo.

Adverse Events Occurring Among Duloxetine Delayed-Release Capsules -Treated Patients in Placebo-Controlled Fibromyalgia (FM) Trials

Table 6 lists the incidence of treatment-emergent adverse events (TEAEs) that occurred in ≥2% of patients treated with duloxetine delayed-release capsules in the fibromyalgia (FM) placebo-controlled trials and with an incidence greater than placebo. The following TEAEs had an incidence in the duloxetine delayed-release capsules treatment group ≥5.0% and were significantly more frequent with duloxetine delayed-release capsules than with placebo: nausea, headache, dry mouth, insomnia, fatigue, constipation, diarrhoea, dizziness, somnolence, hyperhidrosis, and decreased appetite.

Table 6: Treatment-Emergent Adverse Events Incidence in the FM Placebo-Controlled Trials*

System Organ Class / Adverse Reaction	Percentage of Patients Reporting Reaction	
	Placebo (N=535)	Duloxetine Delayed-Release Capsules (N=876)
Cardiac Disorders		
Palpitations	2	2
Eye Disorders		
Vision blurred	1	2
Gastrointestinal Disorders		
Nausea	11	29
Dry mouth	5	18
Constipation	4	15
Diarrhea	8	12
Dyspepsia	3	5

System Organ Class / Adverse Reaction	Percentage of Patients Reporting Reaction	
	Placebo (N=535)	Duloxetine Delayed-Release Capsules (N=876)
General Disorders and Administration Site Conditions		
Fatigue[a]	8	15
Immune System Disorders		
Seasonal allergy	2	3
Infections and Infestations		
Upper respiratory tract infection	6	7
Urinary tract infection	3	3
Influenza	2	2
Gastroenteritis viral	2	2
Investigations		
Weight increased	1	2
Metabolism and Nutrition Disorders		
Decreased appetite[b]	2	11
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain	4	5
Muscle spasms	3	4
Nervous System Disorders		
Headache	12	20
Dizziness	7	11
Somnolence[c]	3	11
Tremor	1	4
Paresthesia	4	4
Migraine	3	3
Dysgeusia	1	3
Psychiatric Disorders		
Insomnia[d]	10	16
Agitation[e]	2	6

System Organ Class / Adverse Reaction	Percentage of Patients Reporting Reaction	
	Placebo (N=535)	Duloxetine Delayed-Release Capsules (N=876)
Sleep disorder	2	3
Abnormal dreams[f]	1	3
Orgasm abnormal[g]	<1	3
Libido decreased[h]	<1	2
Reproductive System and Breast Disorders		
Ejaculation disorder[1,l]	0	4
Penis disorder[1]	0	2
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	3	4
Pharyngolaryngeal pain	3	3
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	1	7
Rash	2	4
Pruritus	2	3
Vascular Disorders		
Hot flush	2	3

* Events reported by at least 2% of patients treated with duloxetine delayed-release capsules and more often than with placebo. The following events were reported by at least 2% of patients treated with duloxetine delayed-release capsules for FM and had an incidence equal to or less than placebo: nasopharyngitis, back pain, sinusitis, anxiety, arthralgia, depression, pain in extremity, vomiting, pain, abdominal pain, bronchitis, abdominal pain upper

[1] Male patients only (N = 46 duloxetine-treated patients versus 26 placebo patients)

[a] Also includes asthenia

[b] Also includes anorexia

[c] Also includes hypersomnia and sedation

[d] Also includes middle insomnia, early morning awakening, and initial insomnia

[e] Also includes feeling jittery, nervousness, restlessness, tension, and psychomotor agitation

[f] Also includes nightmare

[g] Also includes anorgasmia

[h] Also includes loss of libido

[l] Also includes ejaculation failure and ejaculation dysfunction

Dose Dependency of Adverse Events in Fibromyalgia

In one fibromyalgia study the most common adverse events that occurred in the duloxetine 120 mg QD group at an incidence rate that was 5% or greater, and approximately twice that of the duloxetine 60 mg/day group included the following: constipation (21.1% versus 10.0%; p=.01) and somnolence (15.0% versus 7.3%, p=.043).

In another fibromyalgia study somnolence was the most common adverse event that occurred in the duloxetine 60 mg BID group at an incidence rate that was 5% or greater, and approximately twice that of the duloxetine 60 mg QD group (12.1% versus 5.1%, p=.064).

Adverse Events Occurring Among Duloxetine Delayed-Release Capsules-Treated Patients in Placebo-Controlled CLBP Trials

Table 7 lists the incidence of treatment-emergent adverse events (TEAEs) that occurred in ≥2% of patients treated with duloxetine delayed-release capsules in the CLBP placebo-controlled trials and with an incidence greater than placebo. The most commonly observed adverse events in duloxetine delayed-release capsules-treated CLBP patients (incidence 5% or greater and at least twice the incidence in placebo patients) included nausea, insomnia, somnolence, constipation, dry mouth, fatigue, and dizziness.

Table 7: Treatment-Emergent Adverse Events Incidence in the CLBP Placebo-Controlled Trials*

System Organ Class / Adverse Reaction	Percentage of Patients Reporting Reaction	
	Placebo (N=441)	Duloxetine Delayed-Release Capsules (N=600)
Gastrointestinal Disorders		
Nausea	3	16
Dry mouth	2	9
Constipation	2	7
Diarrhea	4	6
Abdominal Pain[1]	2	3
Flatulence	-	-
General Disorders and Administration Site Conditions		

System Organ Class / Adverse Reaction	Percentage of Patients Reporting Reaction	
	Placebo (N=441)	Duloxetine Delayed-Release Capsules (N=600)
Fatigue (including asthenia)	1	6
Infections and Infestations		
Influenza	3	4
Metabolism and Nutrition Disorders		
Decreased appetite (including anorexia)	<1	4
Musculoskeletal and Connective tissue Disorders		
Musculoskeletal pain (including myalgia and neck pain)	2	3
Nervous System Disorders		
Somnolence (including hypersomnia and sedation)	1	8
Dizziness	2	6
Headache	-	-
Psychiatric Disorders		
Insomnia[2]	4	8
Libido decreased (including loss of libido)	1	3
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	1	3

* Events reported by at least 2% of patients treated with duloxetine delayed-release capsules and more often than placebo. The following events were reported by at least 2% of patients treated with duloxetine delayed-release capsules and CLBP and had an incidence equal to or less than placebo: arthralgia; and nasopharyngitis

[1] Also includes abdominal pain upper, abdominal discomfort, and gastrointestinal pain

[2] Also includes initial insomnia, middle insomnia, terminal insomnia

Adverse Events Occurring Among Duloxetine Delayed-Release Capsules-Treated Patients in Placebo-Controlled OA Trials

Table 8 lists the incidence of treatment-emergent adverse events (TEAEs) that occurred in ≥2% of patients treated with duloxetine delayed-release capsules in three placebo-controlled OA trials (treatment duration = 10 to 13 weeks) with an incidence greater than placebo. The most commonly observed adverse events in duloxetine delayed-release capsules-treated OA patients (incidence 5% or greater and at least twice the incidence in placebo patients) were: nausea, constipation, dry mouth, diarrhea, abdominal pain, fatigue, dizziness, insomnia, decreased appetite and erectile dysfunction.

Table 8: Treatment-Emergent Adverse Events in Clinical Trials of Patients with Pain due to Osteoarthritis of the Knee.

System Organ Class / Adverse Reaction	Percentage of Patients Reporting AEs	
	Placebo (N = 508)	Duloxetine Delayed-Release Capsules (N = 503)
Gastrointestinal Disorders		
Nausea	3	12
Constipation	2	7
Dry mouth	2	7
Diarrhea	3	6
Abdominal pain[a]	1	5
Vomiting	1	2
Flatulence	<1	2
General Disorders and Administration Site Conditions		
Fatigue [b]	1	7
Nervous System Disorders		
Dizziness	2	5
Somnolence [c]	3	5
Headache	3	5
Psychiatric Disorders		
Insomnia [d]	2	5
Libido decreased	<1	2

System Organ Class / Adverse Reaction	Percentage of Patients Reporting AEs	
	Placebo (N = 508)	Duloxetine Delayed-Release Capsules (N = 503)
Metabolism and nutrition disorders		
Decreased appetite	<1	5
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	<1	4
Musculoskeletal and connective tissue disorders		
Arthralgia	2	2
Reproductive system and breast disorders		
Erectile dysfunction [f]	1	5
Ejaculation disorder [e,f]	0	3

a. Also includes Abdominal discomfort, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Gastrointestinal pain.
b. Also includes Asthenia
c. Also includes Hypersomnia, Sedation.
d. Also includes Initial insomnia, Middle insomnia, Terminal insomnia.
e. Also includes Ejaculation failure
f. Male only (N=173 for Placebo, N=192 for Duloxetine).

Other Adverse Events

Urinary Hesitation: Duloxetine delayed-release capsules are in a class of drugs known to affect urethral resistance during the filling stage of the bladder. Spontaneous post-marketing cases of urinary hesitation and retention have been reported. In some instances of urinary retention associated with duloxetine delayed-release capsules therapy, hospitalization and/or catheterization was required. If symptoms of urinary hesitation develop during treatment with AG-Duloxetine, consideration should be given to the possibility that they might be drug-related. Dose-reduction or discontinuation should also be considered (see 7 Warnings and Precautions: Renal; Urinary Hesitation and Retention).

Gastrointestinal Bleeding: In placebo-controlled clinical trials across all indications, gastrointestinal hemorrhage was reported in 0.23% of duloxetine delayed-release capsules-treated patients compared with 0.15% of placebo-treated patients (p=.198). The term gastrointestinal hemorrhage is a combined term consisting of diarrhea hemorrhagic, lower

gastrointestinal hemorrhage, hematemesis, hematochezia, hemorrhoidal hemorrhage, melena, rectal hemorrhage, and ulcer hemorrhage. A statistically significant difference in the incidence of gastrointestinal hemorrhage between duloxetine delayed-release capsules-treated patients compared with placebo-treated patients was only seen in MDD placebo-controlled trials (duloxetine delayed-release capsules 0.3% [9/3007 patients] versus 0.05% [1/1883 patients], p=.031) but not the other indications. In fibromyalgia placebo-controlled trials, 0.44% (5/1139) patients experienced gastrointestinal bleeding compared to 0.12% (1/802) patients in the placebo arm; this difference was not statistically significant (p = .328). Post-marketing cases of gastrointestinal bleeding have also been reported (see 8.5 Post-Market Adverse Reactions).

Laboratory Changes: Duloxetine delayed-release capsules treatment in placebo-controlled clinical trials across indications was associated with small mean increases from baseline to endpoint in ALT, AST, CPK, and alkaline phosphatase; infrequent, transient, abnormal values were observed for these analytes in duloxetine delayed-release capsules-treated patients, compared with placebo-treated patients (see 7 Warnings and Precautions: Hepatic/Biliary/Pancreatic). In placebo-controlled clinical trials across all indications, treatment-emergent high potassium levels were observed more frequently in duloxetine-treated patients than placebo patients (2.2% with duloxetine versus 1.6% with placebo, p=.016). In addition, the treatment-emergent adverse event “Blood potassium increased”, including the individual terms Hyperkalemia and Blood potassium increased, was reported more frequently in duloxetine-treated patients than placebo patients (0.11% with duloxetine versus 0.05% with placebo, p=.146).

Vital Sign Changes: In placebo-controlled clinical trials across all approved indications for change from baseline to endpoint, duloxetine delayed-release capsules treatment was associated with mean increases of 0.09 mm Hg in systolic blood pressure and 0.65 mm Hg in diastolic blood pressure compared to mean decreases of 1.35 mm Hg systolic and 0.79 mm Hg diastolic in placebo-treated patients.

Sustained elevations of either systolic or diastolic blood pressure were also measured in placebo-controlled studies. A patient was considered to have sustained elevation in blood pressure if either of the following criteria for sustained elevation in systolic blood pressure or diastolic blood pressure was met.

- Sustained elevation in systolic blood pressure was defined as a value ≥140 mm Hg with an increase ≥10 mm Hg from baseline for three consecutive visits.
- Sustained elevation in diastolic blood pressure was defined as a value ≥90 mm Hg with an increase of ≥10 mm Hg from baseline for three consecutive visits.

In placebo-controlled trials across all approved indications, there was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure.

There was no significant difference between treatment groups in the frequency of elevated blood pressure as a reason for discontinuation.

Duloxetine delayed-release capsules treatment, for up to 26 weeks in placebo-controlled trials across all approved indications, was associated with an increase in heart rate of 1.39 beats per minute (mean change from baseline to endpoint).

Weight Changes: Duloxetine delayed-release capsules had minimal effect on weight. In MDD and GAD placebo-controlled clinical trials, patients treated with duloxetine delayed-release capsules for up to 9 weeks experienced a mean weight loss of approximately 0.5 kg, compared with a mean weight gain of approximately 0.35 kg in placebo-treated patients. This represents a small but significant decrease in weight compared with placebo-treated patients. Long-term trials over 52 weeks in duration demonstrated a mean weight gain of 2.4 kg but this was not clinically significant.

In DPN, FM, CLBP and OA studies, patients treated with duloxetine delayed-release capsules (N=3160) for up to 26 weeks experienced a mean weight loss of approximately 0.63 kg compared with a mean weight gain of approximately 0.15 kg in placebo-treated patients.

In 3 placebo-controlled DPN clinical trials, patients treated with duloxetine delayed-release capsules for up to 13 weeks experienced a mean weight loss of 0.92 kg, compared with a mean weight gain of 0.16 kg in placebo-treated patients. In long-term trials of up to 52 weeks in duration, the mean decrease in weight was 0.35 kg for duloxetine delayed-release capsules-treated patients.

In FM studies, patients treated with duloxetine delayed-release capsules for up to 26-weeks experienced a mean weight loss of approximately 0.4 kg compared with a mean weight gain of approximately 0.3 kg in placebo-treated patients. In one long-term FM 60-week uncontrolled study, (195 patients completed the study) duloxetine delayed-release capsules patients had a mean weight increase of 0.7 kg.

In one long-term CLBP 54-week study (13-week, placebo-controlled acute phase and 41-week uncontrolled extension phase), duloxetine delayed-release capsules-treated patients (N=109) experienced a mean weight decrease of 0.6 kg compared with a mean weight increase of 0.1 kg in placebo-treated patients (N=116) during the acute phase of the study. In the open-label phase, all patients treated with duloxetine delayed-release capsules (N=178) had a mean weight increase of 0.4 kg.

Glucose Regulation: In DPN trials, duloxetine delayed-release capsules treatment worsened glycemic control in some diabetic patients. In three clinical trials of duloxetine delayed-release capsules for the management of pain associated with DPN, the mean duration of diabetes was

approximately 12 years, the mean baseline fasting blood glucose was 9.8 mmol/L (176 mg/dL), and the mean baseline hemoglobin A1c (HbA1c) was 7.8%. In the 12-week acute treatment phase of these studies, duloxetine delayed-release capsules were associated with a small increase in mean fasting blood glucose as compared to placebo. In the extension phase of these studies, which lasted up to 52 weeks, mean fasting blood glucose increased by 0.67 mmol/L (12 mg/dL) in the duloxetine delayed-release capsules group and decreased by 0.64 mmol/L (11.5 mg/dL) in the routine care group, which was statistically different. HbA1c increased by 0.5% in the duloxetine delayed-release capsules group and by 0.2% in the routine care groups.

Sexual Dysfunction: Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and healthcare professionals may be reluctant to discuss them. Table 9 displays the incidence of sexual side effects spontaneously reported by at least 2% of either male or female patients taking duloxetine delayed-release capsules in MDD placebo-controlled trials.

Table 9: Treatment-Emergent Sexual Dysfunction-Related Adverse Events Incidence in MDD Placebo-Controlled Trials[1]

Adverse Event	Percentage of Patients Reporting Event			
	% Male Patients		% Female Patients	
	Duloxetine Delayed-Release Capsules (N=378)	Placebo (N=247)	Duloxetine Delayed-Release Capsules (N=761)	Placebo (N=530)
Orgasm abnormal[2]	4	1	2	0
Ejaculatory dysfunction[3]	3	1	NA	NA
Libido decreased	6	2	1	0
Erectile dysfunction	4	1	NA	NA
Ejaculation delayed	3	1	NA	NA

1 Events reported by at least 2% of patients treated with duloxetine delayed-release capsules and more often than with placebo.
2 Term includes anorgasmia.
3 Term includes ejaculation disorder and ejaculation failure.

NA=Not applicable

The incidence of treatment-emergent sexual dysfunction-related events (TEAEs) that occurred in ≥2% of patients treated with duloxetine delayed-release capsules and with an incidence greater than placebo in the placebo-controlled trials for other indications are presented in the tables above for GAD, DPN, FM, CLBP and OA trials.

Prescribers should routinely inquire about possible sexual adverse events during treatment with AG-Duloxetine.

8.3 Less Common Clinical Trial Adverse Reactions

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

The following is a list of treatment-emergent adverse reactions reported by patients treated with duloxetine in clinical trials. In clinical trials across all indications, 34,756 patients were treated with duloxetine. Of these, 26.9% (9337) took duloxetine for at least 6 months, and 12.4% (4317) for at least one year. The following listing is not intended to include reactions (1) already listed in previous tables or elsewhere in labelling, (2) for which a drug cause was remote, (3) which were so general that they were 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: common adverse reactions are those occurring in at least 1/100 patients; uncommon adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in less than 1/1000 patients.

Cardiac Disorders — *Common:* palpitations; *Uncommon:* myocardial infarction, tachycardia.

Ear and Labyrinth Disorders — *Common:* vertigo; *Uncommon:* ear pain, tinnitus.

Endocrine Disorders — *Rare:* hypothyroidism.

Eye Disorders — *Uncommon:* diplopia, visual impairment, mydriasis, dry eye.

Gastrointestinal Disorders — *Common:* flatulence; *Uncommon:* eructation, gastritis, halitosis, gastroenteritis; *Rare:* gastric ulcer, melena, stomatitis.

General Disorders and Administration Site Conditions — *Common:* chills (includes rigors); *Uncommon:* falls (falls were more common in the elderly, ≥ 65 years old), feeling abnormal, feeling hot and/or cold, malaise, thirst, dysphagia; *Rare:* gait disturbance.

Infections and Infestations — Uncommon: laryngitis.

Investigations — *Uncommon:* weight increased, blood cholesterol increased.

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

Musculoskeletal and Connective Tissue Disorders — *Common:* musculoskeletal pain; *Uncommon:* muscle tightness (includes musculoskeletal stiffness), muscle twitching.

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

Psychiatric Disorders — *Common:* abnormal dreams (includes nightmares), sleep disorder; *Uncommon:* apathy, bruxism, disorientation (includes confusional state), irritability, mood swings, suicide attempt; *Rare:* completed suicide.

Renal and Urinary Disorders — *Common:* Urinary frequency; *Uncommon:* dysuria, micturition urgency, nocturia, polyuria, urine flow decreased, urine odour abnormal.

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

Respiratory, Thoracic and Mediastinal Disorders — *Common:* Oropharyngeal pain; *Uncommon:* throat tightness.

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

Vascular Disorders — *Common:* flushing (includes hot flush); *Uncommon:* peripheral coldness, orthostatic hypotension.

8.4 Abnormal Laboratory Findings

Electrocardiogram Changes: Electrocardiograms were obtained from duloxetine delayed-release capsules-treated patients and placebo-treated patients in clinical trials across all indications. No clinically significant differences were observed for QTc, QT, PR, and QRS intervals between duloxetine delayed-release capsules-treated and placebo-treated patients. There were no differences in clinically meaningful QTcF elevations between duloxetine delayed-release capsules and placebo.

Additionally, a clinical pharmacology study was conducted to assess the safety of duloxetine at the highest tolerable level of exposure of duloxetine (200 mg BID) and to measure QT interval. QT interval at doses up to 200 mg BID was not prolonged (see 10.2 Pharmacodynamics: Cardiac Electrophysiology Study).

8.5 Post-Market Adverse Reactions

Since the first approval of duloxetine delayed-release capsules on 03 August 2004 through 31 July 2013, it is estimated that 63.8 million patients have been treated with duloxetine delayed-release capsules worldwide, accounting for over 23.8 million patient-years of therapy.

Hepatic: Post-marketing surveillance has identified reports of hepatic injury, including hepatocellular, pure cholestatic and mixed injury ranging from mild elevations in laboratory values to more severe clinical signs and symptoms of liver injury. Isolated cases of liver failure, including fatal cases, have been reported. Most of these cases have been reported in patients with past or current medical and other risk factors for liver injury, including alcohol abuse, hepatitis, or exposure to drugs with known adverse effects on the liver and it is unclear to what extent duloxetine may have played a contributing role (see 2 Contraindications and 7 Warnings and Precautions: Hepatic/Biliary/Pancreatic).

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

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. More severe and/or acute cases have been associated with hallucination, syncope, seizure, coma, respiratory arrest, and death (see 7 Warnings and Precautions: Renal).

Gastrointestinal bleeding: Post-marketing cases of gastrointestinal bleeding have been reported very rarely (Table 10) (see also 8.2 Clinical Trial Adverse Reactions: Other Adverse Events, Gastrointestinal Bleeding).

Serious Dermatological Reactions: There have been very rare post-marketing reports of serious cutaneous reactions including Stevens-Johnson Syndrome (SJS) and erythema multiforme in patients treated with duloxetine delayed-release capsules (see 7 Warnings and Precautions: Skin). Post-market reporting rate is generally accepted to be an underestimate due to under-reporting. In some cases, causality in relation to duloxetine delayed-release capsules could not be established. Patients should be advised that if they experience a skin rash, they should discontinue AG-Duloxetine treatment and contact their healthcare professional for assessment and advice.

Acute pancreatitis: Cases of acute pancreatitis have been reported with SSRIs and SNRIs, including duloxetine. Although causality could not be established due to confounding factors, a role for duloxetine could not be excluded.

Table 10 is based on post-market spontaneous adverse event reports. The percentages shown are calculated by dividing the number of adverse events reported to the company by the estimated number of patients exposed to the drug during the same time period. A causal relationship between duloxetine delayed-release capsules and the emergence of these events has not been clearly established.

Table 10: Duloxetine Delayed-Release Capsules Post-Market Spontaneous Adverse Event Reports For All Indications

Adverse Event	Frequency			
	Common ≥1%	**Uncommon <1% and ≥0.1%**	**Rare <0.1% and ≥0.01%**	**Very Rare <0.01%**
Blood Disorders				
Thrombocytopenia				X
Cardiac Disorders				
Supraventricular arrhythmia				X
Cardiac failure exacerbation				X
Cardiomyopathy				X
Ear and Labyrinth Disorders				
Tinnitus upon treatment discontinuation				X

Adverse Event	Frequency			
	Common ≥1%	**Uncommon <1% and ≥0.1%**	**Rare <0.1% and ≥0.01%**	**Very Rare <0.01%**
Endocrine Disorders				
Syndrome of Inappropriate Antidiuretic Hormone (SIADH)				X
Eye Disorders				
Glaucoma				X
Gastrointestinal Disorders				
Gastrointestinal bleeding				X
Hematochezia			X	
Microscopic colitis				X
Hepatobiliary Disorders				
Hepatitis				X
Jaundice				X
Immune System Disorders				
Anaphylactic reaction				X
Hypersensitivity				X
Investigations				
Alanine aminotransferase increased				X
Alkaline phosphatase increased				X
Aspartate aminotransferase increased				X
Bilirubin increased				X
Metabolism and Nutritional Disorders				
Hyponatremia				X
Hyperglycemia (reported mostly in diabetic patients)				X
Musculoskeletal and connective tissue disorders				
Muscle spasm				X

Adverse Event	Frequency			
	Common ≥1%	**Uncommon <1% and ≥0.1%**	**Rare <0.1% and ≥0.01%**	**Very Rare <0.01%**
Trismus				X
Nervous System Disorders				
Extrapyramidal disorder				X
Paresthesia (including electric shock-like sensation) upon treatment discontinuation				X
Restless leg syndrome				X
Serotonin syndrome				X
Seizures				X
Seizures upon treatment discontinuation				X
Psychiatric Disorders				
Hallucinations			X	
Mania				X
Aggression and anger (particularly early in treatment or after treatment discontinuation)				X
Renal and Urinary Disorders				
Urinary retention			X	
Reproductive System and Breast Disorders				
Galactorrhea				X
Gynecological bleeding				X
Hyperprolactinemia				X
Testicular pain				X
Skin and Subcutaneous Tissue Disorders				
Rash			X	
Alopecia				X
Angioneurotic edema				X
Contusion				X
Cutaneous vasculitis (sometimes associated				X

Adverse Event	Frequency			
	Common ≥1%	Uncommon <1% and ≥0.1%	Rare <0.1% and ≥0.01%	Very Rare <0.01%
with systemic involvement)				
Ecchymosis				X
Erythema multiforme				X
Stevens-Johnson Syndrome				X
Urticaria				X
Vascular Disorders				
Orthostatic hypotension (especially at initiation of treatment)				X
Syncope (especially at initiation of treatment)				X
Hypertensive crisis				X

9 Drug Interactions

9.1 Serious Drug Interactions

Serious Drug Interactions

- **Monoamine Oxidase Inhibitors: See 2 Contraindications and 9.4 Drug-Drug Interactions**
- **Thioridazine: See 2 Contraindications** and **9.4 Drug-Drug Interactions**
- **Potent CYP1A2 Inhibitors: See 2 Contraindications** and **9.4 Drug-Drug Interactions**

9.2 Drug Interactions Overview

Patients should be advised to inform their healthcare professionals if they are taking, or plan to take, any prescription or over-the-counter medications.

Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Concomitant of AG-Duloxetine with potent CYP1A2 inhibitors (e.g. fluvoxamine) and some quinolone antibiotics (e.g. ciprofloxacin or enoxacin) is contraindicated (see 2

Contraindications). Duloxetine should be administered with caution with CYP2D6 inhibitors (see 9.4 Drug-Drug Interactions).

Duloxetine is a moderate inhibitor of CYP2D6. Duloxetine should be administered with caution with medications that are predominately metabolized by the CYP2D6 system or have a narrow therapeutic index such as antiarrhythmics (see 9.4 Drug-Drug Interactions).

Duloxetine is highly bound to plasma proteins (>90%). Administration of AG-Duloxetine with another drug that is highly protein bound may cause increased free concentrations of either drug (see 9.4 Drug-Drug Interactions).

Concomitant use of other drugs with serotonergic activity (e.g., SNRIs, SSRIs, triptans, or tramadol) may result in serotonin syndrome (see 7 Warnings and Precautions: Neurologic, Serotonin Syndrome/Neuroleptic Malignant Syndrome and 9.4 Drug-Drug Interactions).

Caution is advised when AG-Duloxetine is taken in combination with other centrally acting drugs and substances, especially those with a similar mechanism of action, including alcohol (see 9.3 Drug-Behaviour Interactions and 9.4 Drug-Drug Interactions).

9.3 Drug-Behavioural Interactions

Smoking: AG-Duloxetine bioavailability appears to be about 34% lower in smokers than in nonsmokers, although dosage modifications are not routinely recommended.

Alcohol: Although duloxetine does not increase the impairment of mental and motor skills caused by alcohol, the concomitant use of duloxetine and substantial amounts of alcohol is not recommended.

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 cholestasis. Substantial inter- current ethanol use was present in each of these cases, and this may have contributed to the abnormalities seen (see 7 Warnings and Precautions: Hepatic/Biliary/Pancreatic).

9.4 Drug-Drug Interactions

Potential for Other Drugs to Affect AG-Duloxetine

Inhibitors of CYP1A2: When duloxetine 60 mg was co-administered with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to male subjects (n=14) duloxetine AUC was increased by approximately 6-fold, the C_{max} was increased about 2.5-fold, and duloxetine t½ was increased by

approximately 3-fold. Concomitant use of AG-Duloxetine with potent CYP1A2 inhibitors (e.g. fluvoxamine) and some quinolone antibiotics (e.g. ciprofloxacin, or enoxacin) is contraindicated (see 2 Contraindications).

Inhibitors of CYP2D6: Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 would be expected to, and does, result in higher concentrations (on average 60%) of duloxetine. Paroxetine (20 mg QD) increased duloxetine (40 mg QD) AUC and C_{max} by 60%. Caution is advised if administering duloxetine with inhibitors of CYP2D6 (e.g., SSRIs).

Dual Inhibition of CYP1A2 and CYP2D6: Concomitant administration of duloxetine 40 mg BID 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_{max}.

Potential for Duloxetine to Affect Other Drugs

Monoamine Oxidase Inhibitors (MAOIs): In patients receiving a serotonin reuptake inhibitor in combination with a MAOI, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued serotonin reuptake inhibitors and are then started on a MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. The effects of combined use of duloxetine delayed-release capsules (duloxetine hydrochloride) and MAOIs have not been evaluated in humans or animals. Therefore, because AG-Duloxetine is an inhibitor of both serotonin and norepinephrine reuptake, it is recommended that AG-Duloxetine not be used in combination with a MAOI, including the antibiotic linezolid and methylene blue, a surgical dye, or within at least 14 days of discontinuing treatment with a MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping AG-Duloxetine before starting a MAOI (see 2 Contraindications: MAOIs and 9.1 Serious Drug Interactions).

Thioridazine: Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias, and sudden death. This effect appears to be dose-related.

An *in vivo* study suggests that drugs which inhibit P4502D6, including certain SSRIs such as paroxetine, fluoxetine, and fluvoxamine, will elevate plasma levels of thioridazine. Therefore, as duloxetine delayed-release capsules are a moderate inhibitor of CYP2D6 and increases the AUC and C_{max} of drugs metabolized by CYP2D6, Duloxetine should not be used in combination with thioridazine. (See 2 Contraindications and 9.1 Serious Drug Interactions).

Drugs Metabolized by CYP2D6: Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine (60 mg BID) was co-administered with a single 50-mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. The co-administration of duloxetine (40 mg BID) increased steady-state AUC of tolterodine (2 mg BID) by 71% but did not affect the pharmacokinetics of the 5-hydroxyl metabolite. Therefore, caution should be used if duloxetine is co-administered with medications that are predominately metabolized by the CYP2D6 system or have a narrow therapeutic index such as antiarrhythmics (e.g., flecainide and encainide) (see 9.4 Drug-Drug Interactions: Tricyclic Antidepressants).

Drugs Metabolized by CYP1A2: *In vitro* drug interaction studies demonstrate that duloxetine does not induce catalytic activity associated with the CYP1A2 isoform. Therefore, an increase in the metabolism of CYP1A2 substrates (e.g., theophylline and caffeine) resulting from induction is not anticipated, although clinical studies of induction have not been performed. Duloxetine has been shown to be a potential inhibitor of the CYP1A2 isoform in *in vitro* studies. However, in a clinical study, the pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by co-administration with duloxetine (60 mg BID). These results suggest that duloxetine is unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates.

Drugs Metabolized by CYP2C9: Results of *in vitro* studies demonstrate that duloxetine does not inhibit CYP2C9 activity.

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

Drugs Metabolized by CYP2C19: Results of *in vitro* studies demonstrate that duloxetine does not inhibit CYP2C19 activity at therapeutic concentrations. Inhibition of the metabolism of CYP2C19 substrates is therefore not anticipated, although clinical studies have not been performed.

CNS Drugs: Caution is advised when AG-Duloxetine is taken in combination with other centrally acting drugs and substances, especially those with a similar mechanism of action, including alcohol. Concomitant use of other drugs with serotonergic activity (e.g., SNRIs, SSRIs, triptans, or tramadol) may result in serotonin syndrome.

Drugs Highly Bound to Plasma Protein: Duloxetine is highly bound to plasma proteins (>90%). Therefore, administration of AG-Duloxetine to a patient taking another drug that is highly protein bound may cause increased free concentrations of either drug.

Electroconvulsive Therapy (ECT): There are no clinical studies of the combined use of electroconvulsive therapy and duloxetine.

Benzodiazepines

Lorazepam: Under steady-state conditions, duloxetine (60 mg Q 12 hours) had no effect on lorazepam (2 mg Q 12 hours) pharmacokinetics and lorazepam had no effect on duloxetine pharmacokinetics. The combination of duloxetine and lorazepam resulted in increased sedation compared with lorazepam alone.

Temazepam: Under steady-state conditions, duloxetine (60 mg qhs) had no effect on temazepam (2 mg qhs) kinetics and temazepam had no effect on duloxetine pharmacokinetics.

Serotonergic Drugs: Based on the mechanism of action of duloxetine and the potential for serotonin syndrome, caution is advised when AG-Duloxetine is coadministered with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as tryptophan, triptans, serotonin reuptake inhibitors, lithium, tramadol, fentanyl and its analogues, dextromethorphan, tapentadol, meperidine, methadone, pentazocine or St. John's Wort (see 7 Warnings and Precautions: Neurologic, Serotonin Syndrome/Neuroleptic Malignant Syndrome).

Triptans (5HT1 agonists): Cases of life-threatening serotonin syndrome have been reported during combined use of selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans. If concomitant treatment with AG-Duloxetine and a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see 7 Warnings and Precautions: Neurologic, Serotonin Syndrome/Neuroleptic Malignant Syndrome).

Tricyclic Antidepressants (TCA): Caution is advised in the co-administration of tricyclic antidepressants (TCAs) (e.g. amitriptyline, desipramine, nortriptyline) with duloxetine, because duloxetine may inhibit TCA metabolism. 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 (see 9.4 Drug-Drug Interactions: Drugs Metabolized by CYP2D6).

Drugs Affecting Platelet Function (e.g., NSAIDs, ASA, and other anticoagulants): Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID, ASA or other anticoagulants may potentiate this risk of bleeding.

Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully

monitored when AG-Duloxetine is initiated or discontinued (see 7 Warnings and Precautions: Hematologic).

Potential for Interaction with Drugs that Affect Gastric Acidity: AG-Duloxetine has 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, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using AG-Duloxetine in patients with conditions that may slow gastric emptying (e.g. some patients with diabetic gastroparesis). Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. However, co-administration of duloxetine delayed-release capsules with aluminum- and magnesium-containing antacids (51 mEq) or duloxetine delayed-release capsules with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40-mg oral dose. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption.

9.5 Drug-Food Interactions

Food delays the time for duloxetine to reach peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11%) (see 10.3 Pharmacokinetics: Absorption). However, food does not affect the C_{max} of duloxetine. AG-Duloxetine may be taken with or without food.

9.6 Drug-Herb Interactions

In common with other SSRIs and SNRIs, pharmacodynamic interactions between duloxetine and the herbal remedy St. John's Wort may occur and may result in an increase in undesirable effects. Interactions with other herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 Clinical Pharmacology

10.1 Mechanism of Action

Duloxetine (duloxetine hydrochloride) is a serotonin and norepinephrine reuptake inhibitor, and weakly inhibits dopamine uptake with no significant affinity for histaminergic, dopaminergic, cholinergic, and adrenergic receptors. Duloxetine is also a potent in vitro inhibitor of transporter binding, with 5-HT and transporter NE inhibition constants (Ki) of 0.8 and 7.5 nM, respectively. Duloxetine dose-dependently increases extracellular levels of serotonin and norepinephrine in various brain areas of animals. The exact mechanism of action of duloxetine in humans is unknown. It is chemically unrelated to other SNRIs, tricyclic, tetracyclic, or other available drugs effective in the treatment of MDD.

10.2 Pharmacodynamics

The effectiveness of duloxetine in the treatment of MDD is presumed to be linked to inhibition of central nervous system (CNS) neuronal uptake of serotonin and norepinephrine, and a resultant increase in serotonin and norepinephrine neurotransmission. The pain inhibitory action of duloxetine is believed to be a result of potentiation of descending inhibitory pain pathways within the central nervous system. Studies at clinically relevant doses in humans (i.e., 40-60 mg BID) have shown that duloxetine decreases 5-hydroxytryptamine concentration in the blood and decreases the urinary excretion of norepinephrine and its metabolites, consistent with blockade of serotonin and norepinephrine uptake processes, respectively. Duloxetine undergoes extensive metabolism; however, the major circulating metabolites have not been shown to contribute significantly to the pharmacologic activity of duloxetine. Neurochemical and behavioural studies in laboratory animals showed an enhancement of both serotonin and norepinephrine neurotransmission in the CNS. Responses consistent with enhanced serotonergic and noradrenergic neurotransmission include lowered food intake, body weight, and alcohol intake. Duloxetine also normalized pain thresholds in several preclinical models of neuropathic [L5/L6 spinal nerve ligation model and partial sciatic nerve ligation model] and inflammatory pain [carrageenan model and acetic-acid induced writhing model] and attenuated pain behaviour in a model of persistent pain [formalin model, late phase] at doses that are consistent with *in vivo* blockade of 5HT and NE reuptake sites].

Duloxetine's affinity for dopamine uptake sites is low. Nevertheless, animal studies have shown increases in extracellular levels of dopamine in prefrontal cortex in addition to increases in norepinephrine and serotonin levels. This is presumed to be associated with the known propensity of cortical norepinephrine transporters to take up dopamine as well as norepinephrine, rather than an effect on dopamine transporters themselves.

Cardiac Electrophysiology Study

A clinical pharmacology study was conducted to assess the safety of duloxetine at the highest tolerable level of exposure of duloxetine and measure QT interval. Of the 117 subjects enrolled, 84 were available for statistical analysis at the maximum dosage of 200 mg BID, and 91 on placebo. Seventy subjects (approximately 60%) completed the entire protocol. Compared with placebo, the mean change in the QTcF interval decreased at each time point with duloxetine 200 mg BID, ranging between -3.0 and -6.4 msec. The upper limit of the two-sided 90% confidence intervals was less than 5 msec at each time point, indicating no clinically relevant increase in the QTcF interval. Similar results were found with the covariance approach and the individual correction method.

No individual QTcF exceeded 470 msec on either duloxetine or placebo, and only 2 subjects had a categorical QTcF increase >30 msec at either 160 mg BID or 200 mg BID dosages (n=84), compared with 6 subjects (n=97) at placebo. Furthermore, no subject had a maximal QTc interval greater than 450 msec based on the average of replicate QTcF and QTcI values on day four of duloxetine 200 mg BID. The ability to detect relevant changes in QTc intervals in this

study was confirmed by observing significant differences in the QTc interval at two time points (mean change in QTcF = 6.7 msec at 2 hours, p<0.0001 and 2.7 msec at 6 hours, p=0.0186) with moxifloxacin as compared with placebo. QT interval at doses up to 200 mg BID was not prolonged.

10.3 Pharmacokinetics

Absorption: In humans, orally administered duloxetine hydrochloride is well absorbed, with maximal plasma concentrations (C_{max}) of duloxetine occurring 6 hours post dose. Food does not affect the C_{max} of duloxetine. However, food delays the time to reach peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11%).

Duloxetine plasma exposure increases in proportion to dose for doses up to 60 mg twice a day. Steady-state plasma concentrations are typically achieved after 3 days of dosing. Based upon AUC, multiple once daily doses of 60 mg produce steady-state concentrations that are approximately 1.5 times higher than that predicted from a 60 mg single dose. Average minimum and maximum steady-state concentrations for the 60 mg QD dose are 27.0 and 89.5 ng/mL, respectively. There is no clinically important difference in the pharmacokinetic parameters of morning and evening doses.

Distribution: The apparent volume of distribution ranges from 701 to 3800 L (5th to 95th percentile, mean of 1640 L). Duloxetine is highly bound (>90%) to proteins in human plasma, binding primarily to albumin and α1-acid glycoprotein. Plasma protein binding of duloxetine is not affected by renal or hepatic impairment.

Metabolism: Biotransformation and disposition of duloxetine in humans have been determined following oral administration of ^{14}C-labelled duloxetine. Integrated over time, duloxetine comprises about 3% of the total radiolabelled 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 CYP2D6 and CYP1A2 catalyze the formation of 2 major metabolites found in plasma and urine (glucuronide conjugate of 4-hydroxy duloxetine, and the sulfate conjugate of 5-hydroxy,6-methoxy duloxetine). The major circulating metabolites are not pharmacologically active.

Excretion: The elimination half-life of duloxetine ranges from 8.1 to 17.4 hours (5th to 95th percentile, mean of 12.1 hours) and the apparent plasma clearance ranges from 33 to 261 L/hr (5th to 95th percentile, mean of 101 L/hr). Apparent plasma clearance of duloxetine does not differ between once daily and twice daily dosing. Only trace (<1% of the dose) amounts of unchanged duloxetine are present in the urine following single dose administration of 14C-labelled duloxetine. The majority (72%) of the duloxetine dose is recovered in the urine as metabolites of duloxetine and approximately 19% is recovered in the feces.

Special Populations and Conditions

- **Pediatrics:** Safety and efficacy in pediatric patients have not been established.

  In a Phase 2, 6-month, open-label pharmacokinetic, safety and tolerability study in pediatric patients (ages 7-17 years) with MDD, duloxetine delayed-release capsules 30 mg QD to 120 mg QD was administered to 72 patients. The median steady state duloxetine concentrations in pediatric patients receiving 60 mg QD duloxetine were ~29% lower than in previous data for adults. Duloxetine apparent oral clearance (CL/F) in pediatric patients was nearly twice the value estimated from previous data in adults. Similarly, median body weight normalized CL/F was nearly four times and two times higher in children and adolescents respectively, as compared with adults. The pharmacokinetic results in pediatric patients from this study and the comparison with adults should be considered preliminary. Health Canada has not authorized an indication for pediatric use (see 3 Serious Warnings and Precautions Box, 4.2 Recommended Dose and Dosage Adjustment: General Considerations for Dosing in Special Populations and 7 Warnings and Precautions: Psychiatric).
- **Geriatrics:** The pharmacokinetics of duloxetine after a single dose of 40 mg were evaluated in 12 healthy elderly females (65 to 77 years) and 12 healthy middle-age females (32 to 50 years). There was no difference in the C_{max}, but the AUC of duloxetine was 24% higher and the half-life 4.3 hours longer in the elderly females. Pharmacokinetic results suggest no overall differences between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Dosage adjustment based on the age of the patient is not necessary (see 4.2 Recommended Dose and Dosage Adjustment: General Considerations for Dosing in Special Populations and 7.1.4 Geriatrics).
- **Sex:** In clinical pharmacology studies, the mean apparent clearance of duloxetine was 9 to 55% lower in females as compared with males. In these studies, duloxetine half-life was similar between males and females. A similar effect of gender on the apparent plasma clearance was identified in patients with MDD. Since exposure in males and females spans a similar range, these differences in average clearance values do not appear to be clinically significant. Dosage adjustment based on gender is not necessary.
- **Ethnic Origin:** No specific pharmacokinetic study was conducted to investigate the effects of race. Due to large interpatient variability, clinically significant differences in drug level exposure among ethnic groups are not likely.
- **Hepatic Insufficiency:** Patients with clinically evident hepatic impairment have decreased duloxetine metabolism and elimination. After a single, non-therapeutic (20 mg) dose of duloxetine delayed-release capsules, 6 cirrhotic patients with moderate liver impairment (Child-Pugh Class B) had a mean plasma duloxetine clearance about 15% that of age- and gender-matched healthy subjects, with a 5-fold increase in mean exposure (AUC). Although Cmax was similar to normals in the cirrhotic patients, the half-

life was about 3 times longer. AG-Duloxetine is contraindicated in patients with any liver disease resulting in hepatic impairment (see 2 Contraindications: Hepatic Impairment; 4.2 Recommended Dose and Dosage Adjustment: General Considerations for Dosing in Special Populations and 7 Warnings and Precautions: Hepatic/Biliary/Pancreatic).

- **Renal Insufficiency:** Duloxetine Cmax and AUC values were approximately 2-fold higher in patients with end stage renal disease (ESRD) receiving chronic intermittent hemodialysis, compared with subjects with normal renal function. In contrast, the elimination half-life was similar in both groups. Studies have not been conducted in patients with a moderate degree of renal dysfunction. Population PK analyses suggest that mild renal dysfunction has no significant effect on duloxetine apparent clearance. AG-Duloxetine is not recommended for patients with end-stage renal disease or severe renal impairment (see 2 Contraindications: Severe Renal Impairment; 4.2 Recommended Dose and Dosage Adjustment: General Considerations for Dosing in Special Populations and 7 Warnings and Precautions: Renal).
- **Smoking Status:** Duloxetine bioavailability appears to be about 34% lower in smokers than in nonsmokers, although dosage modifications are not routinely recommended.

11 Storage, Stability and Disposal

Store at room temperature, 15-30°C.Keep out of reach and sight of children.

Part 2: Scientific Information

13 Pharmaceutical Information

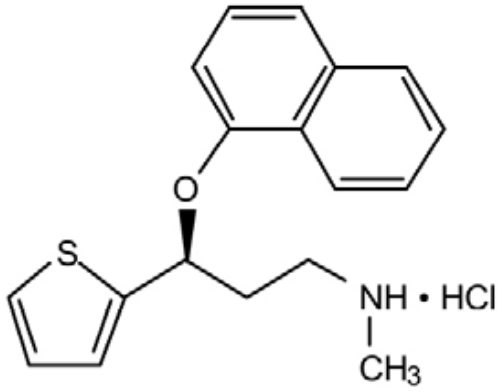
Drug Substance

Proper Name: duloxetine hydrochloride

Chemical Name: (+)-(*S*)-*N*-methyl-γ-(1-naphthalenyloxy)-2-thiophenepropanamine hydrochloride

Molecular formula and molecular mass: $C_{18}H_{19}NOS \bullet HCl$
333.88 g/mol.

Structural Formula:



Physiochemical properties:

Description: White to off white powder

Solubility of duloxetine hydrochloride:

Solvent	**Descriptive USP Term**
Water	Slightly soluble
Ethanol	Freely soluble
Methanol	Freely soluble
Acetone	Slightly soluble

14 Clinical Trials

14.1 Clinical Trials by Indication

Major Depressive Disorder (MDD) Studies

Study Demographics and Trial Design:

The efficacy of duloxetine delayed-release capsules (duloxetine hydrochloride) as a treatment for MDD was assessed in 6 randomized, double-blind, placebo-controlled, fixed-dose studies in adult outpatients (18 to 83 years) meeting DSM-IV criteria for MDD, and having baseline scores of ≥15 on the 17-Item Hamilton Depression Rating Scale and ≥4 on the Clinic Global Impression Severity Score. Primary efficacy was evaluated using the mean total scores of the HAMD17.

In two studies of identical design, 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 a second set of 2 studies of identical design patients were randomized to duloxetine delayed-release capsules 20 mg (N=91 and N=86) or 40 mg twice daily (N=84 and N=91) or placebo (N=90 and N=89) for 8 weeks; in a third set of studies of identical design, patients were randomized to duloxetine delayed-release capsules 40 mg (N=95 and N=93) or 60 mg twice daily (N=93 and N=103) or placebo (N=93 and N=99) for 8 weeks. The design of the six studies is summarized in Table 11.

Table 11: Clinical Trials Supporting Efficacy of Duloxetine Delayed-Release Capsules in the Treatment of MDD

Study #	Trial Design/Duration	Dosage, Route Of Administration	Study Subjects (N) [Female/Male (F/M)]	Mean Age Age Range	Baseline Scores Mean HAMD-17 (Mean CGI-S)
HMBH(a)	9-week, multi centre, parallel, double-blind, randomized, placebo-controlled, fixed dose; double-blind placebo lead-out	Duloxetine 60 mg PO QD	N=245 [F=163; M=82]	Mean age = 42.4 Age range = 18.6-77.7	21.3 (4.3)
HMBH(b)	9-week, multi centre, parallel, double-blind, randomized, placebo-controlled, fixed dose; double-blind placebo	Duloxetine 60 mg PO QD	N=267 [F=184; M=83]	Mean age = 40.9 Age range =	20.4 (4.2)

Study #	Trial Design/Duration	Dosage, Route Of Administration	Study Subjects (N) [Female/Male (F/M)]	Mean Age Age Range	Baseline Scores Mean HAMD-17 (Mean CGI-S)
	lead-out			19.2-82.9	
HMAT(a)	8-week, multicentre, parallel, double-blind, randomized, placebo- and active comparator-controlled study with blinded placebo lead-in and placebo lead-out	Duloxetine 20 mg or 40 mg PO BID Paroxetine 20 mg QD	N=354 [F=218; M=136]	Mean age = 43.7 Age range = 18.0-82.2	17.7 (3.9)
HMAT(b)	8-week, multi centre, parallel, double-blind, randomized, placebo- and active comparator-controlled study with blinded placebo lead-in and placebo lead-out	Duloxetine 20 mg or 40 mg PO BID Paroxetine 20mg QD	N=353 [F=217; M=136]	Mean age = 40.5 Age range = 18.2-78.2	17.9 (4.1)
HMAY(a)	8-week, multi centre, parallel, double-blind, randomized, placebo- and active comparator-controlled study with blinded placebo lead-in and placebo lead-out with 26-week continuation phase	Duloxetine 40 mg or 60 mg PO BID Paroxetine 20 mg QD	Acute Phase: N=367 [F=267; M=100] Continuation Phase: N=273 [F=199; M=100]	Acute Phase: Mean age = 43.4 Continuation Phase: Mean age = 42.9	20.0 (4.3)
HMAY(b)	8-week, multi centre, parallel, double-blind, randomized, placebo- and active comparator-controlled study with blinded placebo lead-in and placebo lead-out with 26-week continuation phase	Duloxetine 40 mg or 60 mg PO BID Paroxetine 20 mg QD	Acute Phase: N=392 [F=273; M=119] Continuation Phase: N=293 [F=204; M=89]	Acute Phase: Mean age = 45.2 Continuation Phase: Mean age = 45.1	21.1 (4.3)

Study Results:

The $HAMD_{17}$ total score was the primary efficacy measure for the assessment of duloxetine delayed-release capsule's effectiveness in the treatment of MDD. Additional secondary efficacy measures that supported the emotional and physical symptoms of MDD included: $HAMD_{17}$ Depressed Mood Item (Item 1), $HAMD_{17}$ Core and Anxiety subscales, Global Impression Scales (Patient Global Impressions (PGI) Improvement and CGI-Severity), and the Quality of Life in Depression (QLDS) rating scale.

In four of the six studies, duloxetine delayed-release capsules demonstrated statistical superiority over placebo as measured by improvement in the 17-item Hamilton Depression Rating Scale (HAMD-17) total score (see Table 12). The secondary efficacy outcomes were supportive of the primary efficacy outcomes.

Table 12: Mean Change in Hamilton Depression Rating Scale (HAMD-17) Total Score

Study	Duloxetine Delayed-Release Capsules	Placebo	p-value
HMBH(a)	-9.47 (60 mg QD)	-5.67	p≤0.001
HMBH(b)	-8.75 (60 mg QD)	–7.02	p<0.05
HMAT(b)	-6.08 (20 mg BID) -6.77 (40 mg BID)	-3.67	p≤0.05 p≤0.01
HMAY(a)	-10.22 (40 mg BID) -11.06 (60 mg BID)	-8.07	p≤0.01 p≤0.001

In comparison with placebo, duloxetine delayed-release capsules at doses of 60 mg once daily and 40 mg and 60 mg twice daily produced a significantly higher rate of response and remission as defined respectively by ≥50% decrease in the HAMD-17 total score and a total endpoint HAMD-17 score of ≤7.

There was no evidence that doses of greater than 60 mg/day conferred any additional benefit.

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.

Study in Elderly Patients with Depression:

In a study comparing duloxetine delayed-release capsules 60mg QD (n=207) and placebo (n=104) in the acute treatment (study duration 8 weeks) of elderly patients with MDD (>65

years of age, mean age 72.9 years), the efficacy of duloxetine delayed-release capsules 60 mg once a day in treating depression symptoms was demonstrated by a statistically significant difference in the reduction of the HAMD17 score for duloxetine-treated patients compared to placebo ($p<0.001$). Tolerability of duloxetine delayed-release capsules 60 mg once daily in elderly patients in this study was comparable to that seen in younger adults, but greater sensitivity of some older individuals cannot be ruled out.

Long-Term Maintenance of Effect Studies:

The efficacy of duloxetine delayed-release capsules in maintaining antidepressant effect was assessed in two long-term studies.

Study HMBC*:* Patients responding to 12 weeks of acute treatment with open-label duloxetine delayed-release capsules at a dose of 60 mg once daily were randomly assigned to either duloxetine delayed-release capsules 60 mg once daily or placebo for a further 6 months (continuation phase) and time to relapse in each group was compared. Of 533 subjects who enrolled in the study, 278 responded and were randomized to duloxetine delayed-release capsules 60 mg once daily (n=136) or placebo (N=142). Response during the open-label phase was defined as meeting the following criteria at weeks 10 and 12: a HAMD-17 total score ≤9, Clinical Global Impressions of Severity (CGI-S) ≤2, and not meeting the DSM-IV criteria for MDD. The estimated probability of depressive relapse at 6 months for duloxetine delayed-release capsules was 19.7% and for placebo was 38.3% ($p=0.004$). During the 6-month continuation therapy phase of this study, 17.4% of duloxetine delayed-release capsules-treated patients met the *a priori*-defined criteria for relapse compared with 28.5% on placebo. Median duration of treatment was 64 days for placebo and 178 days for duloxetine, with 74 (54%) patients on duloxetine and 47 (33%) patients on placebo completing the 6 month, double-blind continuous phase. Relapse during the continuation phase was defined as an increase in the CGI-S score of ≥2 points compared with that obtained at week 12, as well as meeting the DSM-IV criteria for MDD at 2 consecutive visits at least 2 weeks apart, where the 2-week temporal criterion had to be satisfied at only the second visit.

Study HMDI*:* Patients with at least 3 episodes of MDD in the past 5 years (and were in remission between the episodes) who responded to duloxetine delayed-release capsules at a dose of 60 to 120 mg QD during an initial 4- to 10-week, open-label, acute treatment period, and who continued to respond to the same dose during a further 24-week, open-label, continuation treatment period, were randomized to duloxetine delayed-release capsules or placebo for a 52-week, double-blind, maintenance phase. Response during the acute and continuation phases was defined as: $HAMD_{17}$ total score ≤9, a CGI-S score ≤2, and not meeting DSM-IV criteria for MDD. During the maintenance phase, patients continued on the duloxetine delayed-release capsules dose to which they had responded (N=146) or underwent a 4-week down-titration to placebo (N=142). For the purposes of this study, recurrence during the maintenance phase was defined as: CGI-S score >4 and meeting DSM-IV criteria for MDD for at least 2 weeks; or 3 consecutive visits that met re-emergence criteria (CGI-S score >4 but not meeting DSM-IV

criteria for MDD) or 10 total re-emergence visits; or discontinued due to lack of efficacy. Time to depressive recurrence, as defined in the study (see above), was statistically significantly longer in duloxetine delayed-release capsules-treated patients compared with placebo-treated patients ($p<0.001$) and significantly fewer patients treated with duloxetine delayed-release capsules experienced a return of their depressive symptoms (14.4%) compared to patients treated with placebo (33.1%).

Secondary efficacy measures that supported the primary outcome included: $HAMD_{17}$ total score and subscales, CGI-Severity scale, PGI Improvement scale, and Sheehan Disability Scale (SDS) global functional impairment score.

The criteria for relapse and recurrence used in these studies were specified for these study protocols only; clinical criteria may vary.

Generalized Anxiety Disorder (GAD) Studies

The efficacy of duloxetine delayed-release capsules as a treatment for GAD was assessed in four acute, randomized, double-blind, placebo-controlled studies (duration: 9-10 weeks) in adult outpatients (ages 18 to 84 years) meeting DSM-IV criteria for GAD, and having baseline Hamilton Anxiety Rating Scale (HAMA) total score of ≥18 (moderate severity) and ≥4 on the Clinical Global Impression of Severity Score. The primary efficacy end-point was mean change from baseline to end-point on the HAMA total score versus placebo. Treatment difference was determined by calculating the difference between mean change in anxiety scores at end-point between duloxetine delayed-release capsules and placebo arms (Drug-Placebo; see Table 13). The main secondary efficacy measure was improvement in the Sheehan Disability Scale (SDS) global functional impairment score. The SDS measures the extent to which emotional symptoms disrupt patient functioning in 3 life domains: work/school, social life/leisure activities, and family life/home responsibilities.

Table 13: Clinical Trials Supporting Efficacy of Duloxetine Delayed-Release Capsules in the Treatment of GAD

Study #	Trial Design/ Duration	Dosing Regimen; No. of Patients per Group (n)	Study Patients (N); Gender (M, F); Mean Age (Range)	Completers N (%)	Baseline Mean HAMA-total	Treatment Difference HAMA (p Value)
HMBR	9 Week, double-blind, fixed dose, placebo-controlled study	DLX 60 mg QD: n=168 DLX 120	N=513 [F=348; M=165]	All DLX: 259/338 (77%)	25.3	-4.4 (p<0.001)

Study #	Trial Design/ Duration	Dosing Regimen; No. of Patients per Group (n)	Study Patients (N); Gender (M, F); Mean Age (Range)	Completers N (%)	Baseline Mean HAMA-total	Treatment Difference HAMA (p Value)
	with a single-blind placebo lead-in.	mg QD: n=170 Placebo: n=175	43.8 (18.0-83.5)	Placebo: 130/175 (74%)		
HMDT	10 Week, double-blind, flexible-dose placebo - controlled, study with a single-blind placebo lead-in.	DLX 60 to 120 mg QD: n=168 Placebo: n=159	N=327 [F=202; M=125] 41.6 (19.2-77.2)	All DLX : 93/168 (55%) Placebo: 109/159 (69%)	23.1	-2.2 (p=0.023)
HMDU	10 Week, double-blind, flexible dose, placebo - and active-controlled study.	DLX 60 to 120 mg QD: n=162 Active Control: 75 to 225 mg QD: n=164 Placebo: n=161	N=487 [F=305; M=182] 40.8 (18.6-83.2)	All DLX : 88/162 (54%) Active Control: 102/164 (62%) Placebo: 100/161 (62%)	25.2	-2.6 (p=0.007)
HMDW	10 Week, double-blind, flexible dose, placebo - and active-controlled study.	DLX 20 mg QD: n=84 DLX 60 to 120 mg QD: n=158 Active Control 75 to 225 mg QD: n=169 Placebo: n= 170	N=581 [F=332; M=249] 42.8 (18.1-78.5)	All DLX : 172/242 (71%) Active Control: 122/169 (72%) Placebo: 102/170 (60%)	27.4	-3.7 (p<0.001)
HMDV	Relapse prevention study	DLX 60 to 120 mg	Open-Label:	Double Blind All DLX :	Open-Label:	Open-Label: -

Study #	Trial Design/ Duration	Dosing Regimen; No. of Patients per Group (n)	Study Patients (N); Gender (M, F); Mean Age (Range)	Completers N (%)	Baseline Mean HAMA-total	Treatment Difference HAMA (p Value)
	with a 6-month, open-label flexible dose phase followed by a 6-month, randomized double-blind placebo-controlled phase.	QD: n=216 Placebo: n=213	N=887 [F=541; M=346] Dbl.-Blind: N=429 [F=257; M=172] 43.3 (18.1-79.7)	167/216 (77%) Placebo: 116/213 (55%)	26.4 Dbl.-Blind: 5.5	14.9 (p<0.001) Dbl.-Blind: -5.9 (p<0.001)

Abbr: DLX = duloxetine; QD = once daily.

Study Results: In all 4 studies, duloxetine delayed-release capsules 60 mg to 120 mg once daily demonstrated statistically significant superiority over placebo as measured by improvement in the primary outcome measure, the HAMA total score, and improvement in secondary outcome measures, including the SDS global functional impairment score and the Clinical Global Impression of Change (CGI-Improvement). The results on the other secondary outcome measures were supportive of the positive primary outcome.

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

Maintenance of Response*:* In a long-term, relapse observation study, patients diagnosed with GAD who had responded during an initial 6 months of open-label duloxetine delayed-release capsules treatment, were randomized to receive either their optimized dose of duloxetine delayed-release capsules or placebo in a double-blind phase for an additional 6-months. There were statistically significantly (p<0.001) more relapses on placebo (42%) as compared to duloxetine delayed-release capsules 60 mg to 120 mg once daily (14%) during the double-blind continuation therapy phase.

Study in Elderly Patients with GAD:

Study HMGF*:* The efficacy of duloxetine delayed-release capsules 30 to 120 mg once daily (n=151) versus placebo (n=140) in elderly patients (>65 years, mean age 71.6 years) with GAD was evaluated in a 12-week randomized, double-blind, placebo-controlled, flexible dose study. The primary efficacy endpoint was the HAMA total score at week 10. The key secondary efficacy measure was the improvement in SDS global functional impairment score. At week 10,

duloxetine delayed-release capsules was superior to placebo on least squares mean change from baseline in HAMA total scores (-15.9 vs. -11.7, p<0.001) and in SDS global functional impairment scores (-8.6 vs. -5.4, p<0.001). The efficacy and safety of duloxetine delayed-release capsules 30 to 120 mg once daily in elderly patients with GAD was similar to that seen in younger adult patients but greater sensitivity of some older individuals cannot be ruled out.

Neuropathic Pain Associated with Diabetic Peripheral Neuropathy (DPN) Studies

Study Demographics and Trial Design: The efficacy of duloxetine delayed-release capsules for the management of neuropathic pain associated with DPN was established in three randomized, 12-week, double-blind, placebo-controlled, fixed-dose studies in adult patients (20 to 84 years) having neuropathic pain associated with DPN for at least 6 months. All studies compared duloxetine delayed-release capsules 60 mg once daily or 60 mg twice daily with placebo. One of the studies also compared duloxetine delayed-release capsules 20 mg with placebo. The design of the three studies is summarized in Table 14.

The three studies enrolled a total of 1139 patients, of whom 888 (78%) completed the studies. Patients enrolled had Type 1 or 2 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 0 (no pain) to 10 (worst possible pain). Patients were permitted up to 4 g of acetaminophen per day as needed for pain, in addition to duloxetine delayed-release capsules. Patients recorded their pain daily in a diary.

Table 14: Study Design of Clinical Trials Supporting Efficacy of Duloxetine Delayed-Release Capsules in the Management of Neuropathic Pain Associated with DPN

Study #	Trial Design/ Duration	Dosage, Route Of Administration	Study Subjects (N)	Number of DLX Completers (n) and Completion Rate (%)	Mean Age (Range)
HMAW – Acute	12 week, multi centre, parallel, double-blind, randomized, placebo-controlled study	DLX 20 mg QD DLX 60 mg QD DLX 60 mg BID PBO	N=457 DLX 20 QD: 115 DLX 60 QD: 114 DLX 60 BID: 113 PBO: 115	n=257 75%	60.1 (22.4-79.1)
HMAV(a) – Acute	12 week, multi centre, parallel, double-blind, randomized,	DLX 60 mg QD DLX 60 mg BID PBO	N=334 DLX 60 QD: 114 DLX 60 BID: 112 PBO:	n=163 72%	60.7 (27.6-84.3)

Study #	Trial Design/ Duration	Dosage, Route Of Administration	Study Subjects (N)	Number of DLX Completers (n) and Completion Rate (%)	Mean Age (Range)
	placebo-controlled study		108		
HMAV(b) – Acute	12 week, multi centre, parallel, double-blind, randomized, placebo-controlled study	DLX 60 mg QD DLX 60 mg BID PBO	N=348 DLX 60 QD: 116 DLX 60 BID: 116 PBO: 116	n=196 85%	58.8 (20.4-81.9)

Study Results: The 24-hour average pain severity was the primary efficacy measure for the assessment of duloxetine delayed-release capsule's effectiveness for the management of neuropathic pain associated with DPN. Evidence of efficacy from the primary efficacy measure was confirmed by comprehensive results from the secondary pain and DPN symptom measures.

In all 3 studies, duloxetine delayed-release capsules 60 mg QD and duloxetine delayed-release capsules 60 mg BID were statistically significantly superior to placebo at 12 weeks as assessed by the reduction from baseline in the 24 hour average pain severity ($p<0.001$).

Duloxetine delayed-release capsule's effect on pain was apparent at the first weekly visit. In all studies, a statistically significant difference ($p<0.001$) between duloxetine delayed-release capsules 60 mg QD versus placebo and 60 mg BID versus placebo was observed at the first week of treatment and persisted to week 12.

In all studies, both duloxetine delayed-release capsules 60 mg QD and 60 mg BID were statistically significantly superior to placebo as assessed by response rate, which was defined as a 30% reduction in pain severity (Table 15).

Table 15: 24-Hour Average Pain Severity; 30% Response Rate at Endpoint All Randomized Patients

	Placebo	DLX 20 mg QD	DLX 60 mg QD	DLX 60 mg BID
Study HMAV(a) – Acute	42%	NA	63%[1]	69%[2]
Study HMAV(b) – Acute	49%	NA	77%[2]	73%[3]

Study HMAW – Acute	47%	51%	64%[4]	65%[5]

[1] p=0.003; [2] p<0.001; [3] p=0.002; [4] p=0.01; [5] p=0.007

Secondary measures which further support the efficacy of duloxetine delayed-release capsules in the management of neuropathic pain associated with DPN included: 24-hour worst pain severity, night pain severity, and Patient's Global Impressions of Improvement (PGI-Improvement). In all studies, the results from these secondary measures were statistically significant for both duloxetine delayed-release capsules 60 mg QD and 60 mg BID when compared to placebo.

In HMAW-Acute, there was a statistically significant difference in 24-hour worst pain severity and PGI-Improvement (p<0.001 for both duloxetine delayed-release capsules 60 mg QD and 60 mg BID versus placebo), and for night pain severity (duloxetine delayed-release capsules 60 mg QD, p=0.025 and duloxetine delayed-release capsules 60 mg BID, p<0.001 versus placebo).

In HMAV(a)-Acute, there was a statistically significant difference in 24-hour worst pain severity (duloxetine delayed-release capsules 60 mg QD, p=0.002 and duloxetine delayed-release capsules 60 mg BID, p<0.001 versus placebo) and PGI-Improvement (p<0.001 for both duloxetine delayed-release capsules 60 mg BID and 60 mg QD versus placebo) and night pain severity (duloxetine delayed-release capsules 60 mg QD, p=0.009 and duloxetine delayed-release capsules 60 mg BID, p<0.001 versus placebo).

In HMAV(b)-Acute, there was a statistically significant difference in 24-hour worst pain severity (duloxetine delayed-release capsules 60 mg QD, p=0.002 and duloxetine delayed-release capsules 60 mg BID, p =0.003 versus placebo) and PGI-Improvement (duloxetine delayed-release capsules 60 mg QD, p=0.002 and duloxetine delayed-release capsules 60 mg BID, p<0.001 versus placebo) and night pain severity (duloxetine delayed-release capsules 60 mg QD, p=0.003 and duloxetine delayed-release capsules 60 mg BID, p=0.002 versus placebo).

Summary*:* In controlled DPN clinical trials, duloxetine delayed-release capsules, at doses of 60 mg QD and 60 mg BID, was statistically significantly more effective than placebo in reducing 24-hour average pain severity (primary efficacy measure), 24-hour worst pain severity, night pain severity, and improving PGI scores.

These findings demonstrate the clinical relevance of the reductions in pain severity observed.

Fibromyalgia (FM) Studies

Study Demographics And Trial Design*:* The efficacy of duloxetine delayed-release capsules in the management of pain associated with FM was established in two randomized, double-blind, placebo-controlled studies (HMCA and HMCJ) in 874 adult patients (19-80 years of age). To

enter the study, patients had to have moderate to severe pain, i.e., baseline average pain of the past week prior to study medication of ≥4, and a diagnosis of fibromyalgia based on the American College of Rheumatology criteria (history of widespread pain for 3 months, and pain present at 11 or more out of 18 specific tender points). During the two studies (HMCA and HMCJ) described below, patients were allowed to take acetaminophen up to 4 g per day, as needed, for pain relief.

The primary efficacy end-point for study HMCA was Brief Pain Inventory (BPI) - Modified Short Form that measures severity and interference of pain on function. The Severity scores range from 0 (no pain) to 10 (pain as bad as you can imagine). The Interference scores range from 0 (does not interfere) to 10 (completely interferes). Treatment differences, defined as change in endpoint mean pain scores for duloxetine delayed release capsules versus placebo (drug – placebo), were calculated. Co-primary efficacy end-points for study HMCJ were BPI and PGI-I (Patient Global Impression of Improvement).

Supplemental and secondary efficacy endpoints included Responder Rates (patients reporting at least 30% or 50% reduction in endpoint mean pain score compared to baseline), Clinical Global Impressions of Severity (CGI), Fibromyalgia Impact Questionnaire (FIQ) and BPI Average Interference Score.

The safety and tolerability of duloxetine delayed-release capsules in patients with fibromyalgia were further established in the long term study (HMEH) which enrolled 307 patients for 60 weeks (64% completed this study).

The design of the placebo-controlled studies is summarized in Table 16.

Table 16: Clinical Trials Supporting Efficacy of Duloxetine Delayed-Release Capsules in the Management of pain associated with Fibromyalgia (FM)

Study #	Trial Design/ Duration	Study Subjects (N)	Mean Age (Range)	Number of Completers (% completed)	Mean Baseline Pain Score (SD) and Range	Primary Efficacy (LS mean change)	Treatment Difference (Range)
HMCA	12 week, parallel, double-blind, fixed	N = 354 patients DLX 60 BID: 116 DLX 60	49.6 years (20-80)	DLX 60 QD: 77 (65%) DLX 60 BID: 71 (61%) PBO: 68 (57%)	DLX 60 QD: mean 6.38 (1.41),	BPI DLX60QD: -2.39 (p≤0.001) DLX60BID:	BPI -1.23 to -1.24

Study #	Trial Design/ Duration	Study Subjects (N)	Mean Age (Range)	Number of Completers (% completed)	Mean Baseline Pain Score (SD) and Range	Primary Efficacy (LS mean change)	Treatment Difference (Range)
	dose, placebo-controlled study	QD: 118 PBO: 120			range 4.0-10.0 DLX 60 BID: mean 6.36 (1.60), range 2.0-10.0 PBO: mean 6.47 (1.47), range 4.0-10.0	-2.40 (p≤0.001) PBO: -1.16	
HMCJ	Parallel, double-blind, fixed dose, placebo-controlled study	N = 520 DLX 20/60 QD: 79 DLX 60 QD: 150 DLX 120 QD: 147 PBO: 144	51.0 (19-77)	<u>3-month therapy phase</u> DLX 20 QD: 49(62%) DLX 60 QD: 97(65%) DLX 120 QD: 95(65%) PBO: 84(58%)	DLX 20 QD: mean 6.74 (1.62) DLX60 QD: mean 6.46 (1.41) DLX 120 QD: mean 6.41 (1.59) PBO: mean 6.57 (1.70) Range	<u>BPI</u> DLX 20 QD: -1.92 (p=.097) DLX 60 QD: -2.00 (p=.022) DLX 120 QD: -2.31 (p<0.001) PBO: -1.38 <u>PGI</u>*- DLX 20 QD: 2.85 (p=.009) DLX 60 QD: 3.04 (p=.044) DLX 120	<u>BPI-</u> -0.53 to -0.93 <u>PGI-I</u> -0.35 to -0.55

Study #	Trial Design/ Duration	Study Subjects (N)	Mean Age (Range)	Number of Completers (% completed)	Mean Baseline Pain Score (SD) and Range	Primary Efficacy (LS mean change)	Treatment Difference (Range)
					4.0-10.0 in all arms	QD: 2.89 (p=.004) PBO: 3.39 (3-month therapy phase)	

QD= once daily; BID = twice daily; DLX = duloxetine; PBO = placebo; BPI = Brief Pain Inventory; PGI= Patient Global Impression of Improvement;

*PGI-Improvement scale range from 1 (very much better) to 7 (very much worse).

Study Results

Study HMCA: In this all female, placebo-controlled study, patients were treated with duloxetine delayed-release capsules 60 mg BID, 60 mg QD (total of 234 patients; 63% completed) or placebo (120 patients; 57% completed). The primary efficacy end-point was BPI average pain severity score. At end-point (3 months of therapy), both duloxetine delayed-release capsules 60 mg QD and BID doses were significantly better than placebo with treatment difference of –1.23 ($p \leq 0.001$) and –1.24 ($p \leq 0.001$) respectively. Some patients on duloxetine delayed-release capsules experienced a decrease in pain as early as week 1, which persisted throughout the study. Most supplemental and secondary endpoints were supportive of the primary efficacy measure. A dose-related increase in adverse events and withdrawals due to adverse events was observed.

Study HMCJ: In this controlled study, patients were randomized to duloxetine delayed-release capsules 20, 60, and 120 mg daily (total of 376 patients; 64% completed 3 month therapy phase) or placebo (144 patients; 58% completed 3 month therapy phase). Co-primary efficacy end-points were BPI average pain severity score and PGI-I at the end of 3 months of therapy. Both duloxetine delayed-release capsules 60 and 120 mg once daily doses were significantly better than placebo at end-point for BPI and PGI-I with treatment differences for BPI ranging between –0.62 ($p = 0.02$) for 60 mg QD and –0.93 ($p \leq 0.001$) for 120 mg QD. Some patients on duloxetine delayed-release capsules experienced a decrease in pain as early as week 1, which persisted throughout the study. Most supplemental and secondary endpoints were supportive of the primary efficacy measure. A dose-related increase in adverse events and withdrawals due to adverse events was observed.

Study HMEH: This 60-week study examined the benefit of up-titration in non-responders to duloxetine delayed-release capsules at 60 mg/day. It consisted of an 8-week open-label period, during which all patients received duloxetine delayed-release capsules 60 mg once daily, and a 52-week randomized, double-blind phase. At the end of the open-label phase, response status, defined as at least a 50% reduction in pain score from baseline, was determined. All completers (responders and non-responders) of the open-label phase were then randomized to double-blind treatment with duloxetine delayed-release capsules at either 60 mg once daily or 120 mg once daily. Those who were considered non-responders at the end of the open-label phase, 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 capsules 60 mg. No new safety issues were identified in this study.

Chronic Low Back Pain (CLBP) Studies

Study Demographics and Trial Design: The efficacy of duloxetine delayed-release capsules in the management of CLBP was established in two randomized, double-blind, 12-13 weeks, placebo-controlled studies (HMEN and HMGC) in 637 adult patients (18-89 years of age). To enter the study, patients had to have a clinical diagnosis of CLBP with pain present on most days for at least 6 months and no signs of radiculopathy or spinal stenosis.

The primary efficacy endpoint in both studies was a reduction in pain severity as measured by the BPI 24-hour average pain rating on the 11-point Likert scale (0 = no pain; 10 = worst possible pain). Some of the supplemental and secondary efficacy endpoints were the Patient's Global Impression of Improvement (PGI-I), Responder Rates (patients reporting at least 30% or 50% reduction in endpoint average pain score compared to baseline), and BPI Severity and Interference Score.

The design of the studies is summarized in Table 17.

Table 17: Clinical Trial Supporting Efficacy of Duloxetine Delayed-Release Capsules in the Management of Chronic Low Back Pain

Study #	Trial Design/ Duration	Study Subjects (N)	Mean Age Age Range	Number of Completers (n) and Completion Rate (%)	Mean Baseline Pain Score (SD) and Range	Primary Efficacy (LS mean change from baseline)	Treatment Difference
HMGC	12-week, double-blind,	N = 401 DLX 60 mg QD =	Mean age = 54.14 yrs	DLX: 147 (74.2%) PBO: 156	BPI DLX: 5.84 (1.43)	BPI DLX: -2.48	BPI -0.68

Study #	Trial Design/ Duration	Study Subjects (N)	Mean Age Age Range	Number of Completers (n) and Completion Rate (%)	Mean Baseline Pain Score (SD) and Range	Primary Efficacy (LS mean change from baseline)	Treatment Difference
	parallel, fixed-dose, placebo-controlled	198 PBO = 203	Age range = 18.66-89.30 yrs	(76.8%)	range 4-10 PBO: 5.75 (1.37) Range 4-10	PBO: -1.80 (p=.001)	
HMEN	13-week, double-blind, parallel, flexible-dose, placebo-controlled	N= 236 DLX 60/120 mg QD* = 115 PBO = 121	Mean age= 51.47 yrs Age range= 20.01-84.59 yrs	DLX: 84 (73%) PBO: 98 (81%)	BPI DLX: 5.91 (1.59), range 2-10 PBO: 5.96 (1.66), range 2-10	BPI DLX: -2.32 PBO: -1.50 (p =.004)	BPI -0.82

*Treatment group of 60/120mg QD is the combined population for patients who stayed on 60mg QD or increased to 120mg QD.

QD= once daily; DLX = duloxetine; PBO = placebo; BPI = Brief Pain Inventory

Study Results

Study HMGC: In this fixed-dose study, patients were not permitted to use any other analgesic agent while taking duloxetine delayed-release capsules. After 12 weeks of treatment, patients taking duloxetine delayed-release capsules 60 mg QD had significantly greater pain reduction compared to placebo (see Table 17). Some patients on duloxetine delayed-release capsules experienced pain reduction as early as week one which persisted throughout the study. Most supplemental and secondary efficacy measures were supportive of the primary end-point.

Study HMEN: In this flexible-dose study, patients assigned to duloxetine delayed-release capsules started treatment at a dose of 30 mg once daily for one week to improve tolerability, then increased to 60 mg once daily (QD). After 7 weeks of treatment with duloxetine delayed-release capsules 60 mg QD, patients with sub-optimal response to treatment (<30% pain reduction) and who tolerated duloxetine delayed-release capsules 60 mg once daily had their dose increased to 120 mg. Patients were permitted to continue on their stable therapeutic dose of NSAIDs or acetaminophen while taking duloxetine delayed-release capsules.

After 13 weeks of treatment, patients taking duloxetine delayed-release capsules 60-120 mg daily had a significantly greater pain reduction compared to placebo (see Table 17). Some patients on duloxetine delayed-release capsules experienced pain reduction in the first week after starting the 60 mg dose which continued throughout the 13 weeks of the acute therapy phase. Most supplemental and secondary efficacy measures were supportive of the primary end-point.

Osteoarthritis (OA) Studies

Study Demographics and Trial Design: The efficacy of duloxetine delayed-release capsules in the management of chronic pain associated with osteoarthritis of the knee was established in two, randomized, double-blind, placebo-controlled studies in 780 adult patients (40 to 92 years). To enter these studies, patients had to meet the American College of Rheumatology (ACR) clinical and radiographic criteria for the diagnosis of osteoarthritis of the knee with pain for ≥14 days of each month for 3 months prior to study entry. In both studies, the 11-point Likert scale (0 = no pain; 10 = worst possible pain) was used to measure pain severity. Some of the supplemental and secondary efficacy endpoints were the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Patient's Global Impression of Improvement (PGI-I), Responder Rates (patients reporting at least 30% or 50% reduction in endpoint average pain score compared to baseline), and BPI Severity and Interference Score.

The design of these studies is summarized in Table 18.

Table 18: Clinical Trials Supporting Efficacy of Duloxetine Delayed-Release Capsules in the Management of Pain due to Osteoarthritis of the Knee.

Study #	Trial Design/ Duration	Study Subjects (N)	Mean Age Age Range	Number of Completers (n) and Completion Rate (%)	Mean Baseline Pain Rating (SD) and Range	Primary Efficacy (LS mean change from baseline in BPI or 24-hour average pain rating)	Treatment Difference
HMFG	13 week, multicenter, randomized, double-blind,	N=256 DLX 60/120 mg	Mean age= 62.5 Age	DLX=93 (73%) PBO: 111	DLX60/120: 6.07 (1.39), range 3-10 PBO: 6.14	DLX60/120: -2.29 PBO: -1.61	-0.68

Study #	Trial Design/ Duration	Study Subjects (N)	Mean Age Age Range	Number of Completers (n) and Completion Rate (%)	Mean Baseline Pain Rating (SD) and Range	Primary Efficacy (LS mean change from baseline in BPI or 24-hour average pain rating)	Treatment Difference
	parallel, placebo-controlled flexible-dose study	QD*: 128 PBO: 128	range= 40 – 79 yrs	(87%)	(1.27), range 4-9	(p= 0.005)	
HMGL	10 week, multicenter, randomized, double-blind, parallel, placebo-controlled, flexible-dose study; DLX added on to optimized NSAID regimen	N=524 DLX 60/120 mg QD*: 264 PBO: 260	Mean age= 61.0 Age range= 40 – 92 yrs	DLX: 189 (72%) PBO: 199 (76%)	DLX60/120: 6.27 (1.41), range 2-10 PBO: 6.36 (1.41), range 4-10	DLX60/120: -2.46 PBO: -1.55 (p= <0.001)	-0.91

*Treatment group of 60/120mg QD is the combined population for patients who stayed on 60mg QD or increased to 120mg QD.

QD= once daily; DLX = duloxetine; PBO = placebo; BPI = Brief Pain Inventory

Study HMFG*:* In this 13-week long, flexible-dose study, 256 patients were initially randomized to receive duloxetine delayed-release capsules (128 patients; 73% completed) or placebo (128 patients, 87% completed). Patients had a mean baseline pain rating of 6 on a numerical rating scale ranging from 0 (no pain) to 10 (worst possible pain). Patients randomized to duloxetine delayed-release capsules started treatment at a dose of 30 mg once daily for one week, then increased to 60 mg once daily (QD). After 7 weeks of treatment with duloxetine delayed-release capsules 60 mg QD, patients with sub-optimal response to treatment (<30% pain reduction) had their dose increased to 120 mg for the remainder of the study, while the remaining patients

who responded continued on duloxetine delayed-release capsules 60 mg QD. For efficacy analyses, data from both duloxetine delayed-release capsules doses were combined and compared to placebo. Patients administered duloxetine delayed-release capsules 60/120 mg QD reported significantly greater pain reduction compared to those on placebo as assessed by the primary efficacy end-point, Brief Pain Inventory (BPI) 24-hour average pain rating (Table 18). Secondary efficacy measures were supportive of the primary end-point.

Study HMGL*:* In this 10 week, placebo-controlled, flexible-dose study, patients with OA pain of the knee, who had inadequate pain relief from an optimized dose of NSAID therapy for two weeks, received duloxetine delayed-release capsules 60/120 mg/day or placebo. After 8 weeks of double-blind treatment, duloxetine-treated patients experienced significantly greater pain reduction compared with placebo on the weekly 24 hour average pain rating (primary efficacy measure). Results of the two gatekeeper efficacy end-points, Western Ontario and McMaster Universities (WOMAC) index of osteoarthritis and Patient Global Impression of Improvement (PGI-I) also demonstrated significantly greater improvement in duloxetine delayed-release capsules-treated patients compared with placebo. Secondary efficacy measures (example BPI) were also supportive of the primary endpoint.

14.2 Comparative Bioavailability Studies

A randomized, two-way, single oral dose, crossover, comparative bioavailability study of AG-Duloxetine (as duloxetine hydrochloride) 60 mg delayed-release capsules (Angita Pharma Inc.) with ^{Pr}CYMBALTA® (duloxetine hydrochloride) 60 mg delayed-release capsules (Eli Lilly Canada Inc.), was conducted in healthy, adult male subjects under fasting conditions. Comparative bioavailability data from 52 subjects that were included in the statistical analysis are presented in the following table:

Summary Table of the Comparative Bioavailability Data

Duloxetine (1 x 60 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_{0-T} (ng.hr/mL)	758.89 851.14 (47.71)	741.68 823.63 (44.86)	102.4	95.5–109.7
AUC_{0-I} (ng.hr/mL)	806.84 900.45 (46.98)	787.01 871.54 (44.66)	102.6	95.9–109.7
C_{max}	41.56	40.23	102.9	96.4–109.8

Duloxetine (1 x 60 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
(ng/mL)	44.99 (40.55)	43.71 (38.80)		
T_{max}[3](hr)	6.50 (2.00- 10.00)	6.50 (4.50-12.00)		
$t_{1/2}$ [4](hr)	13.00 (25.92)	12.79 (23.51)		

[1]AG-Duloxetine (duloxetine hydrochloride), delayed-release capsules, 60 mg (Angita Pharma Inc.)

[2] [Pr]CYMBALTA® (duloxetine hydrochloride), delayed-release capsules, 60 mg (ELI LILLY CANADA INC.).

[3] Expressed as median (range) only

[4] Expressed as arithmetic mean (CV%) only

A randomized, two-way, single oral dose, crossover, comparative bioavailability study of AG-Duloxetine (as duloxetine hydrochloride) 60 mg delayed-release capsules (Angita Pharma Inc.) with [Pr]CYMBALTA® (duloxetine hydrochloride) 60 mg delayed-release capsules (Eli Lilly Canada Inc.), was conducted in healthy, adult male subjects under fed conditions. Comparative bioavailability data from 41 subjects that were included in the statistical analysis are presented in the following table:

Summary Table of the Comparative Bioavailability Data

Duloxetine (1 x 60 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_{0-T} (ng.hr/mL)	887.58 1063.65 (64.82)	876.55 1020.97 (56.13)	101.1	94.2-108.5
AUC_{0-I} (ng.hr/mL)	950.58 1135.36 (64.64)	923.92 1075.75 (56.77)	102.7	96.1-109.8
C_{max} (ng/mL)	44.39 50.49 (51.72)	44.66 49.80 (46.24)	99.3	91.9-107.4
T_{max}[3](hr)	8.50 (5.00 - 12.00)	7.50 (6.00 - 11.50)		

Duloxetine (1 x 60 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
$t_{1/2}$[4] (hr)	13.382 (23.94)	13.051 (24.81)		

[1]AG-Duloxetine (duloxetine hydrochloride), delayed-release capsules, 60 mg (Angita Pharma Inc.)

[2] [Pr]CYMBALTA® (duloxetine hydrochloride), delayed-release capsules, 60 mg (ELI LILLY CANADA INC.)

[3] Expressed as median (range) only

[4] Expressed as arithmetic mean (CV%) only

15 Microbiology

No microbiological information is required for this drug product.

16 Non-Clinical Toxicology

General Toxicology:

Acute Toxicology Studies

The primary findings following acute oral administration of duloxetine to mice, rats, dogs, and monkeys were related to central nervous system (CNS) effects (i.e., tremors, convulsions, emesis, mydriasis, salivation, and hyperresponsiveness). In rats and mice, the median lethal dose ranged from 279 mg/kg to 595 mg/kg. No deaths occurred in single-dose studies in dogs or monkeys at doses up to 100 mg/kg, the highest dose tested.

Important toxicologic effects in rats following the dietary administration of duloxetine hydrochloride for 1, 3, or 6 months occurred primarily in the high-dose group of 0.08% or approximately 50 mg/kg. These effects were decreased mean body weight, body weight gain, and food consumption; moderate hepatic microsomal enzyme induction with correlated increased liver weights, and minimal-to-moderate midzonal hepatocellular lipid vacuolation primarily in males.

Subacute and Long-Term Toxicology Studies

Administration of duloxetine to dogs for 1, 6, or 12 months at doses of 3, 10, or 30 mg/kg caused dose-related clinical signs of the CNS as a result of the pharmacologic action of this compound, including decreased food consumption, abnormal stools, emesis, and mydriasis. The frequency of emesis increased in a dose-related manner and was the dose-limiting effect.

Additional findings were related to the liver (hepatic microsomal enzyme induction, increased liver weight, increased liver phospholipid phosphorus, and increased numbers of secondary lysosomes) and were limited primarily to the 30-mg/kg group. Dogs treated with 3 mg/kg had no adverse signs of toxicity.

Other Toxicology Studies

The toxicity of duloxetine following intravenous administration was evaluated in rats and dogs. Administration of duloxetine to male and female Fischer 344 rats via a daily 30-minute intravenous infusion at dose levels of 1, 5, or 10 mg/kg/day resulted in excessive irritation at the injection sites. Systemic toxicity was not observed at a dose of 1 mg/kg/day for 15 days. Similarly, daily intravenous administration of duloxetine over an approximate 30-minute period to beagle dogs at doses of 1, 2.5, or 5 mg/kg/day for up to 15 days resulted in no evidence of systemic toxicity. However, local irritation at the injection sites precluded dosing of the 5-mg/kg/day group for more than 10 days.

Antigenicity studies indicated that the hypersensitivity-eliciting antigenicity of duloxetine in guinea pigs was restricted to active systemic anaphylaxis when immunized with a hapten-protein conjugate with adjuvant. Duloxetine was nonimmunogenic and did not possess hypersensitivity-eliciting antigenicity in mice. As a result, the overall risk of duloxetine causing allergic adverse reactions clinically is considered minimal.

Dependence studies indicated that duloxetine did not demonstrate any dependence-producing potential in monkeys or rats.

Dermal toxicity and dermal and ocular irritancy were determined to assess the occupational hazard of duloxetine. In the rabbit, duloxetine was considered to be nontoxic and a very slight irritant when administered dermally. Duloxetine was also determined to be corrosive ocularly.

Genotoxicity:

Duloxetine demonstrated no mutagenic potential in a battery of genotoxicity tests which included the Ames bacterial mutagenesis assay, the Chinese hamster ovary (CHO) chromosomal aberration assay, the mouse lymphoma cell mutagenesis assay, the *in vivo* mouse micronucleus assay, the rat hepatocyte unscheduled DNA synthesis assay, and the *in vivo* CHO sister chromatid exchange assay.

Carcinogenicity:

Duloxetine was administered in the diet to rats and mice for 2 years. In rats, dietary doses of duloxetine up to approximately 27 mg/kg/day in females (2.0 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) or approximately 36 mg/kg/day in males (2.6 times the MRHD on a mg/m^2 basis) did not cause any increase in incidence of expected or unusual neoplasms or decrease in the latency for any tumour type. Rats receiving dietary

concentrations of approximately 30 mg/kg/day had plasma concentrations of duloxetine that were 3.5 to 12 times the plasma concentrations of patients receiving the MRHD.

In female mice receiving duloxetine at approximately 144 mg/kg/day (5 times MRHD on a mg/m^2 basis), there was an increased incidence of hepatocellular adenomas and carcinomas, but these were considered to be secondary to hepatic enzyme induction with associated centrilobular hypertrophy and vacuolation. Mice receiving dietary concentrations of approximately 144 mg/kg/day had plasma concentrations of duloxetine that were 3 to 11 times the plasma concentrations of patients receiving the MRHD. The relevance of this mouse data in humans is unknown.

Reproductive and Developmental Toxicity:

Reproductive performance was not affected in male rats receiving duloxetine orally at doses up to 45 mg/kg/day or approximately 3.3 times the MRHD on a mg/m^2 basis. In female rats receiving 45 mg/kg/day duloxetine orally (3.3 times the MRHD on a mg/m^2 basis), reproductive toxicity was demonstrated by a decrease in maternal food consumption and body weight, estrous cycle disruption, depressions in live birth indices and progeny survival, and progeny growth retardation. The no-observed-effect level (NOEL) for maternal toxicity, reproductive toxicity, and developmental toxicity in the female fertility study was 10 mg/kg/day (approximately 0.7 times the MRHD on a mg/m^2 basis).

In embryo-fetal development studies in rats and rabbits there was no evidence of teratogenicity following the oral administration of up to 45 mg/kg/day (3.3 times the MRHD on a mg/m^2 basis). In rat reproduction studies, mating and fertility indices and reproductive parameters were not affected by duloxetine administration of up to 30 mg/kg/day (2.2 times the MRHD on a mg/m^2 basis). A decrease in pup survival to 1 day postpartum and a decrease in mean litter body weights during the lactation period occurred following maternal exposure to 30 mg/kg/day (2.2 times the MRHD on a mg/m^2 basis). Increased reactivity was observed in pups following maternal exposure to 10 and 30 mg/kg/day (0.7 and 2.2 times the MRHD on a mg/m^2 basis, respectively). Growth and reproductive performance of the progeny were not affected adversely by maternal duloxetine treatment.

17 Supporting Product Monographs

1. PrCYMBALTA®(Duloxetine delayed release capsules, 30 mg and 60 mg; control 294797, Product Monograph, Eli Lilly Canada Inc. (2025-12-12)

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]AG-Duloxetine

Duloxetine Delayed-Release Capsules

This Patient Medication Information is written for the person who will be taking **AG-Duloxetine**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **AG-Duloxetine**, talk to your healthcare professional.

Serious warnings and precautions box

Self-harm or suicide:

- Antidepressants, such as AG-Duloxetine, may increase the risk of suicidal thoughts and actions in some children, teenagers, or young adults at the beginning of treatment, or when the dose is changed. AG-Duloxetine is not approved for use in children and teenagers.
- **If you have thoughts of harming or killing yourself at any time, tell your healthcare professional or go to a hospital right away.** Close observation by a healthcare professional is necessary in this situation.

New or worsened emotional or behavioural problems:

- When you first start taking AG-Duloxetine or when your dose is adjusted, you may feel worse instead of better. You may feel new or worsened feelings of agitation, hostility, anxiety, or impulsivity.
- During your treatment with AG-Duloxetine, it is important that you and your healthcare professional talk regularly about how you are feeling. They will closely monitor you for signs of new or worsened emotions or behaviours while you are taking AG-Duloxetine.
- You may find it helpful to tell a relative or close friend that you are depressed. Ask them to read this leaflet. You might ask them to tell you if they:
  - think your depression is getting worse, or
  - are worried about changes in your behaviour.
- If your depression worsens or you experience changes in your behaviour, tell your

healthcare professional right away. Do not stop taking AG-Duloxetine on your own.

What is AG-Duloxetine used for:

- **Chronic (ongoing) low-back pain**
- **Chronic (ongoing) osteoarthritis knee pain**
- **Fibromyalgia pain:** a condition with pain in many parts of the body
- **Diabetic nerve pain:**
  - pain that may be burning, stabbing, stinging, shooting, aching or like an electric shock
  - pain may be caused by touch, heat, cold, or pressure
  - there may be loss of feeling in the affected area
- **Depression:**
  - feeling sad, restless, irritable, tired
  - experiencing a change in appetite or weight, difficulty concentrating or sleeping, headaches, unexplained aches and pains
- **Generalized anxiety:** feeling very anxious and worried

How AG-Duloxetine works:

AG-Duloxetine belongs to a group of medicines called serotonin and norepinephrine reuptake inhibitors (SNRIs). AG-Duloxetine increases the levels of two chemical messengers (serotonin and norepinephrine) found naturally in your brain and other parts of your body.

Depression and Anxiety

Depression and anxiety are mental illnesses. They may happen when chemicals in the brain, such as serotonin and norepinephrine, are not in balance. AG-Duloxetine works to help balance these chemicals. This helps to relieve the emotional and physical symptoms of depression and anxiety.

You may notice that your depression or anxiety symptoms feel better within 1 to 4 weeks after starting AG-Duloxetine.

Diabetic Nerve Pain, Fibromyalgia Pain, Chronic Low Back Pain, and Chronic Osteoarthritis Knee Pain

AG-Duloxetine works by increasing the levels of serotonin and norepinephrine. This helps to reduce the pain in these conditions.

You may notice that your pain symptoms feel better within 1 week after starting AG-Duloxetine.

The ingredients in AG-Duloxetine are:

Medicinal ingredient: Duloxetine hydrochloride

Non-medicinal ingredients: Ascorbic acid, hypromellose, hypromellose phthalate, sucrose, sugar spheres, talc and triethyl citrate.

Cap and body: FD&C Blue No. 2, gelatin, iron oxide yellow (60 mg capsule only), sodium lauryl sulphate and titanium dioxide.

Imprinting ink: Butyl alcohol, dehydrated alcohol, FD & C Blue No. 2 (30 mg capsule only), iron oxide yellow (30 mg capsule only), isopropyl alcohol, potassium hydroxide (60 mg capsule only), propylene glycol, purified water (60 mg capsule only), shellac, strong ammonia solution and titanium dioxide.

AG-Duloxetine comes in the following dosage forms:

Capsules (delayed-release); 30 mg and 60 mg duloxetine (as duloxetine hydrochloride).

Do not use AG-Duloxetine if:

- You are younger than 18 years of age
- You are allergic to duloxetine hydrochloride or any of the other ingredients in AG-Duloxetine (see **The ingredients in AG-Duloxetine are:**)
- You have a liver impairment or disorder. A liver disorder is when your liver can no longer carry out its normal function
- You have severe kidney disease
- You have uncontrolled narrow-angle glaucoma
- You are taking or have just stopped taking any of these drugs in the last 14 days:
  - monoamine oxidase inhibitors (MAOI), such as phenelzine or moclobemide, to treat depression
  - linezolid to treat infection(s)
- You have been given a dye called methylene blue during surgery in the last 14 days
- You are on a drug or have been on a drug to manage psychosis (serious mental illness) called thioridazine
- You are taking a medication to treat depression, like fluvoxamine, a potent CYP1A2 inhibitor
- You are taking certain antibiotics, like ciprofloxacin or enoxacin

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take AG-Duloxetine. Talk about any health conditions or problems you may have, including if you:

- Have or have a history of liver, kidney, or heart problems
- Have diabetes
- Have or have a history of seizures

- Have high blood pressure. AG-Duloxetine may raise your blood pressure
- Have low sodium levels in your blood
- Are pregnant, are thinking about getting pregnant, or are breastfeeding
- Drink alcohol or use street drugs. Drinking a large amount of alcohol while taking AG-Duloxetine may lead to serious liver problems and death
- Have an allergy to any medication
- Have a bleeding disorder that makes you more likely to bleed, or if you have low platelet levels (a type of blood cell)
- Have problems urinating
- Have a rare hereditary disease that means you should not eat sugar. AG-Duloxetine contains a type of sugar called sucrose. These diseases include:
  - Fructose intolerance
  - Glucose-galactose malabsorption
  - Sucrose-isomaltase insufficiency

Other warnings you should know about:

Angle-closure Glaucoma

AG-Duloxetine can cause an acute attack of glaucoma. Having your eyes examined before you take AG-Duloxetine could help identify if you are at risk of having angle-closure glaucoma. Seek immediate medical attention if you experience:

- eye pain
- changes in vision
- swelling or redness in or around the eye

Driving and using machines:

AG-Duloxetine may make you feel dizzy or tired, especially just after you start taking it or after the dose is increased. Wait to see how you feel while taking AG-Duloxetine before driving or using machines.

Effects on pregnancy and newborns:

If you are or become pregnant while taking AG-Duloxetine, talk to your healthcare professional about the risks and benefits of various treatment options. It is very important that you keep taking AG-Duloxetine until your healthcare professional tells you to stop.

Some women experienced rapid loss of blood at birth. This happened especially when the medication was taken in the last 30 days of pregnancy.

Some women have given birth earlier than expected. This happened mostly between 35 and 36 weeks of pregnancy.

When pregnant women took drugs in the same group of medications as AG-Duloxetine, some newborn babies had complications at birth. This happened especially when the medication was taken in the last three months of pregnancy.

Some newborns:

- Required breathing support, tube feeding and a longer stay in the hospital
- Had difficulty feeding or breathing, seizures, tense or overly relaxed muscles and were jittery and cried constantly

These symptoms normally go away over time. If your baby experiences any of these symptoms, contact your healthcare professional as soon as possible.

Risk of breaking a bone:

You should tell your doctor if you:

- are elderly and had a recent bone fracture or
- were told you have osteoporosis or risk factors for osteoporosis

Taking AG-Duloxetine may increase your risk of breaking a bone. This is especially true when you first start taking AG-Duloxetine and soon after you stop taking it. Take extra care to avoid falling, especially if you get dizzy or have low blood pressure.

Serotonin syndrome / neuroleptic malignant syndrome (NMS):

This is a rare side effect of the group of medications like AG-Duloxetine. It is life-threatening and can lead to death. It can cause serious changes in how your brain, muscles, digestive system and nervous system work. The reaction is more likely if you take AG-Duloxetine with certain other medications. Please read the box called **Serious side effects and what to do about them**, below.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious drug interactions:

Serious drug interactions with AG-Duloxetine include:

- Monoamine oxidase inhibitors (MAOIs), which are used to treat depression (such as phenelzine, moclobemide, linezolid, methylene blue). Do not take AG-Duloxetine if you are taking an MAOI, or if you have taken an MAOI in the last 14 days.
- Thioridazine, used to manage psychosis.
- Medications known as potent CYP1A2 inhibitors. These include:

- Some antibiotics such as ciprofloxacin and enoxacin.
- Fluvoxamine, used to treat depression.

The following may also interact with AG-Duloxetine:

- Other medications to treat depression such as:
  - selective serotonin reuptake inhibitors (SSRIs) or SNRIs like fluoxetine, venlafaxine and paroxetine
  - tricyclics like amitriptyline and desipramine
- Medications used to treat schizophrenia like olanzapine and risperidone
- Medications used to treat bipolar disorder like lithium
- Medications that can affect blood clotting and increase bleeding such as:
  - oral anticoagulants like warfarin and dabigatran
  - acetylsalicylic acid or ASA
  - nonsteroidal anti-inflammatory drugs (NSAIDs) used to treat pain and fever like ibuprofen and naproxen
- Some medications used to treat patients with irregular heartbeats like flecainide and encainide
- Some medications that affect the chemical messenger serotonin, like:
  - lithium
  - medications containing tryptophan, used to treat bipolar disorder
  - St. John's Wort (also called Hypericum perforatum), an herbal product often used to treat depression
  - a group of medications called triptans used to treat migraines, like sumatriptan and rizatriptan
- Some pain medications in a group of drugs called opioids, like fentanyl, tramadol, tapentadol, meperidine, methadone and pentazocine
- Some medications used to treat cough, like dextromethorphan (a cough syrup)

In general, drink only small amounts of alcohol while you are taking AG-Duloxetine.

How to take AG-Duloxetine:

- Once each day, at about the same time every day.
- **Swallow capsules whole with a drink of water.**
- Take with or without food. Taking it with food can reduce nausea at the start of treatment.
- Take exactly as prescribed. Do NOT give it to anybody else. They may have unwanted side effects that may be serious.
- Do NOT chew, crush or open the capsule. Do NOT mix with liquids or sprinkle on food or drink.

- If you accidentally break or open the capsules, do NOT touch the powder. Wash away any loose powder right away with water. If you get powder in your eyes, rinse them with water right away and contact your healthcare professional.

Usual dose:

The usual adult dose is 60 mg once daily.

Elderly patients with generalized anxiety:

The starting dose is 30 mg once daily. After 2 weeks, your healthcare professional may increase the dose to 60 mg once daily.

Your healthcare professional may adjust the dose during the course of your treatment. Only increase the amount of AG-Duloxetine you are taking if your healthcare professional tells you to.

You should continue to take AG-Duloxetine for several months or longer, as directed by your healthcare professional.

Stopping AG-Duloxetine:

Do NOT stop taking AG-Duloxetine without discussing it with your healthcare professional. This may help you avoid discontinuation symptoms. Follow your healthcare professional's instructions. They may gradually reduce the dose you are taking.

Patients being treated for nerve pain caused by diabetes:

Continue to see your healthcare professional regularly for the proper management of your diabetes. This will help to control your blood sugar levels and prevent further nerve damage. It is important that you continue to do daily foot examinations.

Overdose:

If you think you, or a person you are caring for, have taken too much AG-Duloxetine, contact your healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs and symptoms.

Missed dose:

If you missed a dose of this medication, take it as soon as you remember. But if it is almost time for your next dose, skip the missed dose and continue with your next scheduled dose. Go back to the regular dosing schedule. Do not take two doses at the same time.

Possible side effects from using AG-Duloxetine:

These are not all the possible side effects you may feel when taking AG-Duloxetine. If you experience any side effects not listed here, tell your healthcare professional.

- Constipation
- Diarrhea
- Dizziness
- Dry mouth
- Erectile dysfunction (trouble getting or keeping an erection)
- Feeling tired
- Headache
- Insomnia (trouble falling asleep and / or staying asleep)
- Less appetite
- More sweating
- Nausea
- Pain in the belly
- Sleepiness
- Vomiting (throwing up)

These side effects have been shown to decrease with continued treatment.

Tell your healthcare professional if:

- any of the side effects discussed above affect you severely
- you experience other side effects not listed here

Some of these side effects may be related to the dose you are taking. Your healthcare professional will decide if your dose needs to be changed.

Depression and anxiety may decrease your sexual desire, performance and satisfaction. This medication may further decrease sexual enjoyment.

You may also have symptoms after you stop taking AG-Duloxetine:

- Anxiety
- Diarrhea
- Dizziness
- Feeling tired
- Headache
- Insomnia

- Irritability
- Muscle pain
- Nausea
- Nerve sensations (numbing, tingling, burning or prickling)
- Nightmares
- Sleepiness
- Severe sweating
- Vertigo (feeling of spinning when not moving)
- Vomiting

These symptoms usually go away without treatment. Tell your healthcare professional right away if you have these or other symptoms.

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Rare			
Allergic reactions: skin rash or hives alone		√	
Angle-closure glaucoma: eye pain, changes in vision, and swelling or redness in or around the eye.			√
Hallucinations: seeing or hearing things that are not there		√	
Mania: overactive behaviour and thoughts		√	
New or worsened emotional or behavioural problems: feeling detached, restless, agitated, anger, aggressive, nervous, short-tempered		√	
Problems with urine flow		√	
Severe allergic reaction: rash, hives, itching, swelling of the face, lips, tongue or throat, difficulty swallowing			√

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
or breathing			
Seizures: uncontrollable shaking with fainting or passing out			√
Thoughts of death or suicide: thoughts of hurting yourself or other people			√
Very rare			
Akathisia: feeling of restlessness, unable to sit or stand still		√	
Gastrointestinal bleeding (bleeding in your stomach, small intestines or large bowel): blood or dark colour in stools, blood in vomit		√	
Hyponatremia (low sodium level of blood): headache, feeling tired, weak, confused, difficulty remembering things, combined with achy, stiff, uncoordinated muscles		√	
Liver disorder: skin or eyes turn yellow, dark urine, pain in the belly, nausea, vomiting, lack of appetite		√	
Serotonin Syndrome and Neuroleptic Malignant Syndrome (NMS): a combination of most or all of the following symptoms: high fever, sweating, shivering, diarrhea, nausea, vomiting, muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination, fast heartbeat, changes in blood pressure, confusion, hallucinations, restlessness, and extreme agitation that can lead to fainting (passing out) and coma			√
Unknown			
Erythema multiforme (serious skin reaction): any combination of itchy			√

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
skin, rash, redness, blistering and peeling of the skin and/or the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or joint pain			
High blood sugar levels: need to urinate very often, feeling thirsty and hungry	√		
Low levels of platelets (a type of blood cell): bruises, bleeding, feeling tired and weak		√	
Pancreatitis (inflammation of the pancreas): upper abdominal pain, fever, rapid heart beat, nausea, vomiting, tenderness when touching the abdomen			√
Stevens-Johnson syndrome (serious skin reaction): fever, sore throat, cough, burning eyes followed by swelling of the face and tongue, hives, pain, rash, blistering and peeling of the skin and/or the mouth, nose and eyes			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Keep out of reach and sight of children.
- Keep capsules in their original packaging.
- Store at room temperature, 15-30°C.
- Keep the packaging in a dry place.
- Keep the packaging out of direct sunlight.
- Use capsules before the expiry date on the packaging. Do NOT use capsules after the expiry date.
- Return any expired or leftover medication to your pharmacist.

If you want more information about AG-Duloxetine:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html) or by calling 450-449-9272.

This leaflet was prepared by:
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