PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]APO-LEVOMILNACIPRAN

Levomilnacipran Extended Release Capsules

Extended Release Capsule, 20 mg, 40 mg, 80 mg and 120 mg levomilnacipran (as levomilnacipran hydrochloride), oral

Antidepressant (ATC Code: N06AX)

APOTEX INC.
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RECENT MAJOR LABEL CHANGES

Not applicable

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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.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

APO-LEVOMILNACIPRAN (levomilnacipran extended release capsules) is indicated for the symptomatic relief of major depressive disorder (MDD).

1.1 Pediatrics

Pediatrics (< 18 years): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of levomilnacipran extended release capsules in pediatric patients has not been established; therefore Health Canada has not authorized an indication for pediatric use. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, 7 WARNINGS AND PRECAUTIONS, Potential association with behavioural and emotional changes, including self-harm and 7.1.3 Pediatrics.

1.2 Geriatrics

Caution should be exercised in treating the elderly. Clinical studies of levomilnacipran extended release capsules did not include sufficient numbers of subjects over 65 years of age to determine whether they respond differently from younger subjects. Dose selection for elderly patients should be cautious. See 7.1.4 Geriatrics.

2 CONTRAINDICATIONS

- **Hypersensitivity:** APO-LEVOMILNACIPRAN is contraindicated in patients who are hypersensitive to levomilnacipran, milnacipran or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- **Serotonin toxicity and Monoamine Oxidase Inhibitors (MAOIs):** APO-LEVOMILNACIPRAN should not be used in combination with MAOIs, including linezolid, an antibiotic, methylene blue, a dye used in certain surgeries, or within two weeks of terminating treatment with MAOIs. Treatment with MAOIs should not be started until 2 weeks after discontinuation of APO-LEVOMILNACIPRAN therapy. Co-administration of MAOIs with selective serotonin reuptake inhibitor (SSRI) or serotonin norepinephrine reuptake inhibitor (SNRI) treatment or with other serotonergic drugs can lead to serious, sometimes fatal, drug interactions. Symptoms include tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, rigidity, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. See 4.1 Dosing Considerations, 7 WARNINGS AND PRECAUTIONS, Serotonin toxicity / serotonin syndrome, and 9.4 Drug-Drug Interactions.

- **Cardiovascular:** APO-LEVOMILNACIPRAN should not be used in patients with:

- myocardial infarction or cardiac intervention within the past 12 months
- NYHA Class III or IV congestive heart failure
- uncontrolled tachyarrhythmia
- uncontrolled hypertension
- a history of cerebrovascular accident

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Increased risk of self-harm, harm to others, suicidal thinking and behavior with antidepressants use. Closely monitor all antidepressant-treated patients for clinical worsening and for emergence of agitation-type and/or suicidal thoughts and behaviors. See 7 WARNINGS AND PRECAUTIONS, Potential association with behavioural and emotional changes, including self-harm.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- **Switching to or from Monoamine Oxidase Inhibitor (MAOI) Antidepressants**

  At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with APO-LEVOMILNACIPRAN. Conversely, at least 14 days should be allowed after stopping APO-LEVOMILNACIPRAN before starting an MAOI antidepressant. See 2 CONTRAINDICATIONS and 9.4 Drug-Drug Interactions.

- **Use of APO-LEVOMILNACIPRAN with Other Drugs that Inhibit Monoamine Oxidase such as Linezolid or Methylene Blue**

  Do not start APO-LEVOMILNACIPRAN in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin toxicity. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered. See 2 CONTRAINDICATIONS, 9.4 Drug-Drug Interactions and 7 WARNINGS AND PRECAUTIONS, Serotonin toxicity / serotonin syndrome.

  In some cases, a patient already receiving APO-LEVOMILNACIPRAN therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, APO-LEVOMILNACIPRAN should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for two weeks or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with APO-

LEVOMILNACIPRAN may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue.

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with APO-LEVOMILNACIPRAN is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use. See 7 WARNINGS AND PRECAUTIONS, Serotonin toxicity / serotonin syndrome.

4.2 Recommended Dose and Dosage Adjustment

Initiating Treatment

Adults: The recommended dose range for APO-LEVOMILNACIPRAN is 40 mg to 120 mg once daily. APO-LEVOMILNACIPRAN should be initiated at 20 mg once daily for 2 days and then increased to 40 mg once daily.

In clinical studies, added benefit was not consistently demonstrated for doses greater than 40 mg/day. If the physician, based on clinical judgment, decides a dose increase above 40 mg/day is warranted for an individual patient, the dose may be increased in increments of 40 mg. The maximum recommended dose should not exceed 120 mg/day.

Maintenance/Continuation/Extended Treatment

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Long-term efficacy of levomilnacipran extended release capsules for up to 26 weeks, following response during 20 weeks of acute, open-label treatment, was established in a placebo-controlled trial.

Physicians choosing to use APO-LEVOMILNACIPRAN should periodically reassess patients to determine the need for continued treatment.

Dosing in Special Populations and Conditions

Hepatic Impairment: No dose adjustment is required in patients with mild, moderate or severe hepatic impairment. See 10.3 Pharmacokinetics.

Renal Impairment: Based on a population pharmacokinetic analysis, no dose adjustment is necessary in patients with mild renal impairment (creatinine clearance of 60 to 89 mL/min). For patients with moderate renal impairment (creatinine clearance of 30 to 59 mL/min), the dose should not exceed 80 mg/day. For patients with more severe renal impairment (creatinine clearance of 15 to 29 mL/min) the dose should not exceed 40 mg/day. See 10.3 Pharmacokinetics. APO-LEVOMILNACIPRAN is not recommended for patients with end stage renal disease.

Geriatric Patients (> 65 years of age): No dose adjustment is required in geriatric patients on the basis of age. See 10.3 Pharmacokinetics.

In a multiple-dose clinical pharmacokinetic study, elderly subjects (> 65 years) had a slightly higher exposure (C_{max} by 24% and AUC by 26%) of levomilnacipran than younger subjects (18 to 45 years).

Because levomilnacipran is predominately excreted by the kidney, renal clearance of levomilnacipran should be considered when determining the dose.

Pediatrics (< 18 years of age): Health Canada has not authorized an indication for pediatric use. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, 7 WARNINGS AND PRECAUTIONS, Potential association with behavioural and emotional changes, including self-harm and 7.1.3 Pediatrics.

Sex: No dose adjustment is required based on sex. See 10.3 Pharmacokinetics.

Discontinuing Treatment

Discontinuation symptoms have been reported with discontinuation of serotonergic drugs such as levomilnacipran extended release capsules. Gradual dose reduction is recommended, instead of abrupt discontinuation, whenever possible. Monitor patients for these symptoms when discontinuing APO-LEVOMILNACIPRAN. If intolerable symptoms occur following a dose decrease or upon discontinuation of treatment, consider resuming the previously prescribed dose and decreasing the dose at a more gradual rate. See 7 WARNINGS AND PRECAUTIONS, Discontinuation Symptoms.

4.4 Administration

APO-LEVOMILNACIPRAN should be taken at approximately the same time each day. APO-LEVOMILNACIPRAN should be swallowed whole. Do not open, chew or crush the capsule. APO-LEVOMILNACIPRAN can be taken with or without food. See 9.5 Drug-Food Interactions.

4.5 Missed Dose

In the event that a dose is missed, the patient should take the missed 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 regular time. The patient should not take two doses of APO-LEVOMILNACIPRAN at the same time.

5 OVERDOSAGE

There is limited clinical experience with levomilnacipran extended release capsules overdose in humans. In clinical trials, cases of ingestions up to 360 mg daily were reported with none being fatal.

No specific antidotes for levomilnacipran extended release capsules are known. In case of an overdose, provide supportive care, including close medical supervision and monitoring. Treatment should consist of those general measures employed in the management of

overdosage with any drug. Consider the possibility of multiple drug overdose. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be considered. The high volume of distribution of levomilnacipran suggests that dialysis will not be effective in reducing levomilnacipran plasma concentrations.

For the most recent information in the management of a suspected drug 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, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	Extended Release Capsule 20 mg, 40 mg, 80 mg, 120 mg	Ethyl cellulose, hypromellose, iron oxide black, iron oxide red, iron oxide yellow, povidone, sugar spheres, talc, titanium dioxide and triethyl citrate. Pharmaceutical ink: Ammonium hydroxide, iron oxide black, potassium hydroxide, propylene glycol and shellac.

APO-LEVOMILNACIPRAN is available as capsules for oral administration, containing levomilnacipran hydrochloride equivalent to 20 mg, 40 mg, 80 mg and 120 mg of levomilnacipran.

20 mg: Off white to pale yellow coloured pellets filled in HPMC capsules having opaque yellow cap and opaque white body imprinted 'LEV' on Cap and '20' on Body with Black ink.

40 mg: Off white to pale yellow coloured pellets filled in HPMC capsules having opaque yellow cap and opaque yellow body imprinted 'LEV' on Cap and '40' on Body with Black ink.

80 mg: Off white to pale yellow coloured pellets filled in HPMC capsules having opaque pink cap and opaque white body imprinted 'LEV' on Cap and '80' on Body with Black ink.

120 mg: Off white to pale yellow coloured pellets filled in HPMC capsules having opaque pink cap and opaque pink body imprinted 'LEV' on Cap and '120' on Body with Black ink.

Packaging: APO-LEVOMILNACIPRAN is supplied in the following configurations:

Blister packaging of 30 (3 x 10) tablets, and Bottles of 100 capsules: 20 mg, 40 mg, 80 mg and 120 mg.

7 WARNINGS AND PRECAUTIONS

Discontinuation Symptoms

Patients currently taking APO-LEVOMILNACIPRAN should NOT be discontinued abruptly, due to risk of discontinuation symptoms. At the time that a medical decision is made to discontinue an SSRI or other newer antidepressant drug, a gradual reduction in the dose rather than an abrupt cessation is recommended.

Discontinuation of treatment with APO-LEVOMILNACIPRAN:

There have been reports of adverse events occurring upon discontinuation of serotonergic antidepressants, particularly when discontinuation is abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia, such as electric shock sensations), anxiety, confusion, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Monitor patients for these symptoms when discontinuing APO-LEVOMILNACIPRAN. Reduce the dose gradually whenever possible. See 4.2 Recommended Dose and Dosage Adjustment, Discontinuing Treatment.

General

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 levomilnacipran extended release capsules. 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 APO-LEVOMILNACIPRAN, cannot be excluded, and may be a potential concern for patients with osteoporosis or major risk factors for bone fractures.

Cardiovascular

Inhibition of the reuptake of norepinephrine (NE) and serotonin (5-HT) can lead to cardiovascular effects. Patients with severe cardiac function impairment or with an identified risk of a serious cardiac arrhythmia, uncontrolled hypertension, or severe or

unstable coronary heart disease were excluded from clinical trials with levomilnacipran extended release capsules.

Elevated Blood Pressure and Hypertension

In short-term, placebo-controlled studies in patients with MDD, levomilnacipran extended release capsules (40 mg to 120 mg) was associated with mean increases of 3.0 mmHg in systolic blood pressure (SBP) and 3.2 mmHg in diastolic blood pressure (DBP) after 8 to 10 weeks of treatment, compared to a mean decrease of 0.4 mmHg SBP and no change in DBP in placebo-treated patients. Approximately 10% of levomilnacipran extended release capsules-treated patients experienced a categorical shift in blood pressure from normotensive/prehypertension to Stage I/Stage II hypertension, compared to 7% of placebo-treated patients.

In healthy subjects who had serial blood pressure assessments during steady-state treatment with 120 mg levomilnacipran, the mean difference from placebo in SBP ranged from 3.8 to 7.2 mmHg and the mean difference from placebo in DBP ranged from 6.1 to 8.1 mmHg. See 10.2 Pharmacodynamics.

In patients exposed to one-year, open-label treatment of levomilnacipran extended release capsules (doses from 40 to 120 mg/day), the mean increase from initiation of treatment in SBP was 3.9 mmHg and DBP was 3.3 mmHg. Upward shifts from normal or prehypertension to Stage 1 or 2 hypertension was experienced by 104/800 (13%) of patients.

Sustained Hypertension: Instances of sustained hypertension were more frequent in levomilnacipran extended release capsules-treated patients (see **Table 2**). Dose-dependency was not evident over the 40 to 120 mg dose range studied. For patients who experience a sustained increase in blood pressure while receiving levomilnacipran extended release capsules, discontinuation or other appropriate medical intervention should be considered.

Table 2 - Incidence of Patients with Sustained Hypertension for All Short-Term Clinical Studies

Criteria	Placebo	Levomilnacipran extended release capsules (40-120 mg/day)
Systolic Blood Pressure ≥ 140 mmHg and ≥ 15 mmHg above baseline for 3 consecutive visits	0.2%	0.8%
Diastolic Blood Pressure ≥ 90 mmHg and ≥ 10 mmHg above baseline for 3 consecutive visits	1.1%	1.4%

Levomilnacipran extended release capsules was associated with an increase in blood pressure in pediatric patients with MDD. These increases in blood pressure led to a higher proportion of pediatric patients developing new-onset and sustained hypertension when compared to adults. See 7.1.3 Pediatrics.

Concomitant use of levomilnacipran extended release capsules with drugs that increase blood pressure has not been evaluated and such combination should be used with caution. See 9.4 Drug-Drug Interactions.

Blood pressure should be measured prior to initiating treatment and periodically throughout APO-LEVOMILNACIPRAN treatment. See 7 WARNINGS AND PRECAUTIONS. Pre-existing hypertension and other cardiovascular disease should be treated and stabilized before starting therapy with APO-LEVOMILNACIPRAN. Centrally acting antihypertensives (clonidine, methyldopa, etc.) were not permitted in the clinical studies and may interact with levomilnacipran extended release capsules. See 9.4 Drug-Drug Interactions.

Elevated Heart Rate

SNRIs, including levomilnacipran extended release capsules, have been associated with increased heart rate.

In short-term placebo-controlled clinical studies in patients with MDD, with periodic steady-state ECG assessments at unspecified time points in relation to dosing, levomilnacipran extended release capsules treatment was associated with mean increases in heart rate of 7.2 beats per minute (bpm) for 40 mg and 80 mg/day and 9.1 bpm for 120 mg/day, compared to a mean decrease of 0.3 bpm in placebo-treated patients. In patients exposed to one-year, open-label treatment of levomilnacipran extended release capsules (doses from 40 to 120 mg/day), the mean change from initiation of treatment in heart rate was 9.1 bpm.

In an ECG assessment study in healthy subjects, with serial ECG data collection over the course of a dosing interval, levomilnacipran extended release capsules 120 mg/day was associated with a maximum placebo-adjusted increase from baseline in heart rate of 20.2 bpm. See 10.2 Pharmacodynamics.

Concomitant use of levomilnacipran extended release capsules with drugs that increase heart rate has not been evaluated and the possibility of additive effects should be considered. Levomilnacipran extended release capsules has not been systematically evaluated in patients with a cardiac rhythm disorder. Heart rate should be measured prior to initiating treatment and periodically measured throughout APO-LEVOMILNACIPRAN treatment. See 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests. Pre-existing tachyarrhythmias and other cardiac disease should be treated before starting therapy with APO-LEVOMILNACIPRAN. Patients with serious or uncontrolled tachyarrhythmias, ischemic heart disease, or congestive heart failure should not receive APO-LEVOMILNACIPRAN. See 2 CONTRAINDICATIONS. For patients who experience an increase in heart rate while receiving APO-LEVOMILNACIPRAN discontinuation or other appropriate medical intervention should be considered.

Dependence/Tolerance

Levomilnacipran extended release capsules has not been systematically studied in animals

or humans for its potential for abuse or dependence. There was no evidence suggestive of drug-seeking behavior in the clinical studies. It is not possible to predict on the basis of clinical experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of APO-LEVOMILNACIPRAN (e.g., development of tolerance or drug-seeking behavior).

Driving and Operating Machinery

Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that APO-LEVOMILNACIPRAN therapy does not adversely affect their ability to engage in such activities.

Endocrine and Metabolism

Diabetic Patients
Levomilnacipran extended release capsules has not been systematically evaluated in diabetic patients. Insulin use was not permitted in premarket clinical trials. Treatment with antidepressants in patients with diabetes may alter glycemic control (hypoglycemia and hyperglycemia). APO-LEVOMILNACIPRAN should be used with caution in diabetic patients on insulin or other antidiabetic drugs. See 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests.

Genitourinary

Urinary Hesitation, Retention and Dysuria

The noradrenergic effect of SNRIs including APO-LEVOMILNACIPRAN, can affect urethral resistance. In the controlled short-term studies, rates of obstructive uropathies were higher in patients treated with levomilnacipran (8%) compared to the placebo arm (1%). Dose dependent increases in urinary hesitation (3.6% in 40 mg/day; 4.9% in 80 mg/day; 6.1% in 120 mg/day) were observed, compared to no patients in the placebo group.

Almost all events of dysuria and urinary hesitation occurred in male patients. Caution is advised in the use of APO-LEVOMILNACIPRAN with concomitant medications that may affect voiding (e.g., anticholinergics) and in patients with a history of obstructive urinary disorders and dysuria, notably in male patients with prostatic hypertrophy, prostatitis, and other lower urinary tract obstructive disorders.

If symptoms of urinary hesitation, urinary retention, or dysuria develop during treatment with APO-LEVOMILNACIPRAN, discontinuation or dose-reduction should be considered.

Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs. In many cases, 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. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted can be at greater risk. Discontinuation of APO-LEVOMILNACIPRAN 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 can lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

Hematologic

Abnormal Bleeding

SSRIs and SNRIs, including levomilnacipran extended release capsules, 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. Bleeding events related to SSRIs and SNRIs have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. SSRIs/SNRIs, including levomilnacipran extended release capsules, may increase the risk of postpartum hemorrhage. See 7.1.1 Pregnant Women.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of levomilnacipran extended release capsules 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).

Monitoring and Laboratory Tests

Self-Harm

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. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX and 7 WARNINGS AND PRECAUTIONS, Potential association with behavioural and emotional changes, including self-harm.

Heart Rate and Blood Pressure

Heart rate and blood pressure should be measured prior to initiating treatment with APO-LEVOMILNACIPRAN and periodically throughout treatment. For patients who experience a sustained increase in blood pressure or heart rate while receiving APO-LEVOMILNACIPRAN, discontinuation or other appropriate medical intervention should be considered.

Patients should be told to consult their doctors if they have symptoms associated with acute severe hypertension such as headache (particularly in the back of head/neck when waking

up), stronger heartbeat and possibly more rapid, palpitations, dizziness, easy fatigability, blurred vision, chest pain. See 7 WARNINGS AND PRECAUTIONS, Cardiovascular.

Serum Cholesterol
Clinically relevant increases in total serum cholesterol were recorded in 5% of patients receiving 40 to 120 mg/day of levomilnacipran extended release capsules in short-term clinical trials, and in 7% of patients exposed to one-year, open-label treatment (doses from 40 to 120 mg/day). Periodic measurement of serum cholesterol levels (including a complete lipid profile/fractionation and an assessment of the patient's individual risk factors) should be considered.

Serum Glucose
Cases of altered glycemic control and new onset diabetes mellitus have been reported in patients receiving antidepressants, including levomilnacipran extended release capsules. Patients should be monitored for signs and symptoms of glucose fluctuations. Diabetic patients especially should have their glycaemia carefully monitored.

Neurologic

Seizures

Levomilnacipran extended release capsules has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies. One case of encephalopathy and convulsion was reported in clinical studies with levomilnacipran extended release capsules. Like other antidepressants, APO-LEVOMILNACIPRAN should be prescribed with caution in patients with a seizure disorder.

Serotonin toxicity / serotonin syndrome

Serotonin toxicity also known as serotonin syndrome is a potentially life-threatening condition and has been reported with SSRIs and SNRIs, including levomilnacipran extended release capsules, particularly during combined use with other serotonergic drugs. See 2 CONTRAINDICATIONS, 9.4 Drug-Drug Interactions.

Serotonin toxicity is characterised by neuromuscular excitation, autonomic stimulation (e.g. tachycardia, flushing) and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature >38°C and ocular clonus or inducible clonus.

The concomitant use of APO-LEVOMILNACIPRAN with serotonin precursors (such as tryptophan) is not recommended. See 9.4 Drug-Drug Interactions. If concomitant treatment with APO-LEVOMILNACIPRAN and other serotonergic agents, including a 5-

hydroxytryptamine receptor agonist (triptan), is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. See 9.4 Drug-Drug Interactions. If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

The concomitant use of APO-LEVOMILNACIPRAN with MAOIs intended to treat psychiatric disorders is contraindicated. APO-LEVOMILNACIPRAN capsules should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with a MAOI such as linezolid or intravenous methylene blue in a patient taking levomilnacipran extended release capsules. APO-LEVOMILNACIPRAN should be discontinued before initiating treatment with the MAOI. See 2 CONTRAINDICATIONS, 9.4 Drug-Drug Interactions, and 4.1 Dosing Considerations.

Ophthalmologic

Angle-Closure Glaucoma
As with other antidepressants, levomilnacipran extended release capsules can cause mydriasis which may trigger an angle-closure attack in patients 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, 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 aged 18 to 24 years with psychiatric disorder showed an increased risk of suicidal behaviour with antidepressants compared to placebo.

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behaviour, worsening of depression, and suicidal ideation, especially when initiating therapy or during any change in dose or dosage regimen. The risk of suicide attempt must be considered, especially in depressed patients.

Suicide

The possibility of a suicide attempt in seriously depressed patients is inherent to the illness and may persist until significant remission occurs. Close supervision of patients should accompany initial drug therapy, and consideration should be given to the need for hospitalization of high-risk patients.

The risk of suicide attempt must be considered, especially in depressed patients; the smallest quantity of drug, consistent with good patient management, should be provided to reduce the risk of overdose with this drug. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX and 7 WARNINGS AND PRECAUTIONS, Potential association with behavioural and emotional changes, including self-harm.

Activation of Mania/Hypomania

Symptoms of mania/hypomania were reported in 0.2% of levomilnacipran extended release capsules-treated patients and 0.2% of placebo-treated patients in clinical studies. Activation of mania/hypomania has also been reported in a small proportion of patients with mood disorders who were treated with other antidepressants. As with all antidepressants, use APO-LEVOMILNACIPRAN cautiously in patients with a history or family history of bipolar disorder, mania, or hypomania.

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. It should be noted that APO-LEVOMILNACIPRAN is not approved for use in treating bipolar depression.

Renal

For patients with moderate to severe renal impairment, the pharmacokinetic disposition of

levomilnacipran is significantly altered. Dosage adjustment is necessary in these patients. See 4.2 Recommended Dose and Dosage Adjustment, Dosing in Special Populations and Conditions.

Reproductive Health: Female and Male Potential

- **Function**

Serotonin-norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (see 8.2 Clinical Trial Adverse Reactions, Sexual Function). Patients should be informed that there have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRIs. It is important for prescribers to inquire about sexual function prior to initiation of levomilnacipran extended release capsules and to inquire specifically about changes in sexual function during treatment, because sexual function may not be spontaneously reported.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies in pregnant women. In pre-market clinical studies, serious adverse events were reported in two pregnant women exposed to levomilnacipran extended release capsules (one premature birth and one preeclampsia) out of 6 confirmed pregnancies with adequate follow-up. The causal relationship between levomilnacipran extended release capsules and the emergence of these events has not been established. APO-LEVOMILNACIPRAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Complications following late third trimester exposure to SNRIs

Observational data have provided evidence of an increased risk (less than 2-fold) of postpartum hemorrhage following SSRI/SNRI exposure within the month prior to birth. See 7 WARNINGS AND PRECAUTIONS, Hematologic.

Neonates exposed to SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability and constant crying. These features are consistent with either a direct toxic effect of these classes of drugs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome. See 7 WARNINGS AND PRECAUTIONS, Serotonin toxicity / serotonin syndrome.

Labour and Delivery

The effect of levomilnacipran extended release capsules on labour and delivery in humans is

unknown. APO-LEVOMILNACIPRAN should be used during labour and delivery only if the potential benefits outweigh the potential risks.

7.1.2 Breast-feeding

There are no adequate and well-controlled studies in nursing mothers. It is not known if levomilnacipran is excreted in human milk. Studies have shown that levomilnacipran is excreted into the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from levomilnacipran extended release capsules, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother. Breast feeding by women treated with APO-LEVOMILNACIPRAN should be considered only if the potential benefits outweigh the potential risks to the child.

7.1.3 Pediatrics

Pediatrics (< 18 years): Based on data submitted and reviewed by Health Canada, the safety and efficacy of levomilnacipran extended release capsules in pediatric patients has not been established; therefore Health Canada has not authorized an indication for pediatric use.

Levomilnacipran extended release capsules was not superior to placebo in two adequate and well-controlled 8-week studies conducted in pediatric Major Depressive Disorder patients; one in patients 7 to 17 years and the second in patients 12 to 17 years.

The most commonly observed adverse reactions with levomilnacipran extended release capsules-treated pediatric MDD patients were nausea, tachycardia, vomiting and decreased appetite. See 8.2.1 Clinical Trial Adverse Reactions - Pediatrics.

In these studies, treatment with levomilnacipran extended release capsules was associated with the occurrence of new-onset hypertension (two systolic and/or diastolic BP measurements in the stage I hypertension range and/or one measurement in the stage II range) in 36.2% of treated patients compared with 20.7% of patients randomized to placebo. Elevations in either systolic or diastolic BP leading to measures at or above the stage II hypertension threshold occurred in 12.1% of pediatric patients treated with levomilnacipran extended release capsules and 7.5% of patients randomized to placebo. Sustained hypertension (three or more consecutive systolic or diastolic BP measurements at or above the stage I hypertension threshold) occurred in 15% of pediatric patients treated with levomilnacipran extended release capsules and 4 % of patients randomized to placebo.

Antidepressants may increase the risk of suicidal thoughts and behaviours in pediatric patients. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX and 7 WARNINGS AND PRECAUTIONS, Potential association with behavioural and emotional changes, including self-harm.

7.1.4 Geriatrics

Of the total number of levomilnacipran extended release capsules-treated subjects in the

short-term clinical studies, only 2.8% of patients were 65 or older.

SSRIs and SNRIs, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event. See 7 WARNINGS AND PRECAUTIONS, Hyponatremia and 10.3 Pharmacokinetics.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of levomilnacipran extended release capsules was evaluated in 3317 patients (18 to 78 years of age) diagnosed with MDD who participated in clinical studies. Among the 3317 levomilnacipran extended release capsules-treated patients, 1,583 were exposed to levomilnacipran extended release capsules in short-term, placebo-controlled studies.

A total of 895 patients were exposed to levomilnacipran extended release capsules for at least 6 months and 367 were exposed for one year. In these studies, levomilnacipran extended release capsules was given at doses ranging from 40 to 120 mg once daily and was given without regard to food.

The most commonly observed adverse events in levomilnacipran extended release capsules -treated MDD patients in placebo-controlled studies (incidence ≥ 5% and at least twice the rate of placebo) were: nausea, heart rate increased, erectile dysfunction, hyperhidrosis, constipation, tachycardia, vomiting, and palpitations.

Adverse Events Reported as Reasons for Discontinuation of Treatment

In the short-term placebo-controlled pre-marketing studies for MDD, 9% of the 1,583 patients who received levomilnacipran extended release capsules (40 to 120 mg) discontinued treatment due to an adverse event, compared with 3% of the 1,040 placebo-treated patients in those studies. The most common adverse event leading to discontinuation in at least 1% of levomilnacipran extended release capsules-treated patients in the short-term placebo-controlled studies was nausea (1.5%).

Blood Pressure and Heart Rate

In placebo-controlled clinical studies for change from baseline to endpoint, levomilnacipran extended release capsules treatment was associated with mean increases in blood pressure and heart rate. See 7 WARNINGS AND PRECAUTIONS, Cardiovascular. The most commonly reported cardiovascular adverse events among levomilnacipran extended release capsules-treated patients in the short-term clinical studies included heart rate increased, tachycardia, palpitations, hypertension, hypotension, and blood pressure increased (see **Table 3**).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and

should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table 3 shows the incidence of adverse events that occurred in ≥ 2% of levomilnacipran extended release capsules-treated MDD patients (and greater than placebo-treated patients) in the short-term, placebo-controlled studies.

Table 3 - Adverse Events Occurring in ≥ 2% of levomilnacipran extended release capsules-Treated Patients and Greater than Placebo Treated Patients in Five, Short-term, Phase 3 Placebo-Controlled Studies

	Levomilnacipran extended release capsules 40-120 mg/day N = 1583 (%)	Placebo N = 1040 (%)
Gastrointestinal disorders		
Nausea	17	6
Dry mouth	10	7
Constipation	9	3
Vomiting	5	1
Abdominal Pain	5	3
Nervous system disorders		
Headache[a]	17	14
Dizziness	8	5
Skin and subcutaneous tissue disorders		
Hyperhidrosis	9	2
Rash	2	<1
Cardiac disorders		
Tachycardia[a]	6	2
Palpitations	5	1
Reproductive system and breast disorders[b]		
Erectile dysfunction[b]	6	1
Testicular pain[b]	4	<1
Ejaculation disorder[b]	5	<1
Investigations		
Heart rate increased[a]	6	1
Blood pressure increased[a]	3	1
Psychiatric disorders		
Insomnia[a]	6	4
Anxiety	2	1
Infections and infestations		
Upper respiratory tract infection[a]	5	4
Nasopharyngitis	4	3

	Levomilnacipran extended release capsules 40-120 mg/day N = 1583 (%)	Placebo N = 1040 (%)
Renal and urinary disorders		
Urinary hesitation	4	0
Vascular disorders		
Hot flush	3	1
Hypertension[a]	3	1
Hypotension	3	1
Metabolism and nutrition disorders		
Decreased appetite	3	1

[a] Similar adverse event terms were grouped together
[b] Percentage is relative to the number of patients in the associated demographic sex category.
N = number of patients in the Safety Population

Dose-Related Adverse Events

In pooled data from the short-term placebo-controlled fixed-dose studies, there were no dose-related adverse events (greater than 2% overall incidence) in patients treated with levomilnacipran extended release capsules across the dose range 40 to 120 mg/day, with the exception of erectile dysfunction and urinary hesitation (see Table 4).

Table 4 - Dose-Related Adverse Events in Two Fixed-Dose, Phase 3, Placebo-Controlled Studies

	Levomilnacipran extended release capsules			Placebo N = 362 (%)
	40 mg/day N = 366 (%)	80 mg/day N = 367 (%)	120 mg/day N = 180 (%)	
Urinary hesitation	4	5	6	0
Erectile dysfunction[a]	6	8	10	2

[a] Percentage is relative to the number of patients in the associated demographic sex category.
N = number of patients in the Safety Population

Sexual Function

While sexual dysfunction is often part of depression and other psychiatric disorders, there is increasing evidence that treatment with selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and norepinephrine-reuptake inhibitors (SNRIs) may induce sexual side effects. This is a difficult area to study because patients may not spontaneously report symptoms of this nature.

Table 5 shows the incidence of adverse events associated with sexual dysfunction in levomilnacipran extended release capsules-treated patients in placebo controlled short-term studies.

Table 5 - Adverse Events Associated With Sexual Dysfunction by Sex in Five, Short-term Phase 3 Placebo-Controlled Studies

	Male		Female	
Preferred Term[a]	**Levomilnacipran extended release capsules 40-120 mg/day N = 577 (%)**	**Placebo N = 374 (%)**	**Levomilnacipran extended release capsules 40-120 mg/day N = 1006 (%)**	**Placebo N = 666 (%)**
Erectile dysfunction	6	1	—	—
Ejaculation disorder	5	<1	—	—
Testicular pain	4	<1	—	—
Libido disorder	2	0	<1	<1
Orgasm abnormal	1	0	<1	<1
Sexual dysfunction	1	0	<1	0
Disturbance in sexual arousal	<1	0	0	0

[a] similar adverse event terms were grouped together
N = number of patients in the Safety Population

8.2.1 Clinical Trial Adverse Reactions - Pediatrics

Pediatrics (<18 years): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of levomilnacipran extended release capsules in pediatric patients has not been established; therefore Health Canada has not authorized an indication for pediatric use.

Two adequate and well-controlled 8-week studies were conducted in pediatric MDD patients, one in patients 7 to 17 years and the second in patients 12 to 17 years. Both studies did not meet both primary and secondary endpoints.

The most commonly observed adverse reactions with levomilnacipran extended release capsules-treated pediatric MDD patients were nausea, tachycardia, vomiting and decreased appetite.

Levomilnacipran extended release capsules was associated with an increase in blood pressure in pediatric patients with MDD. These increases in blood pressure led to a higher proportion of pediatric patients developing new-onset and sustained hypertension when compared to adults. See 7.1.3 Pediatrics.

8.3 Less Common Clinical Trial Adverse Reactions

The following listing does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have significant clinical implications, or 5) which occurred at a rate equal to or less than placebo.

Reactions are categorized by body system according to the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients:

Cardiac disorders: frequent: postural orthostatic tachycardia syndrome; infrequent: angina pectoris; supraventricular and ventricular extrasystoles

Eye disorders: infrequent: dry eye; mydriasis; vision blurred; rare: conjunctival hemorrhage

General disorders and administration site conditions: infrequent: chest pain; thirst; rare: drug withdrawal syndrome

Gastrointestinal disorders: frequent: flatulence; infrequent: hematochezia

Injury, poisoning and procedural complications: infrequent: ankle fracture; contusion; hand fracture; joint dislocation; joint injury; laceration; limb injury; post-traumatic neck syndrome; radius fracture; skeletal injury

Investigations: frequent: weight decreased; infrequent: blood cholesterol increased; liver function test abnormal

Nervous System disorders: frequent: migraine; paraesthesia; infrequent: syncope; rare: convulsion; extrapyramidal disorder

Psychiatric disorders: infrequent: agitation; anger; bruxism; worsening of depression; hypomania; panic attack; suicidality (including ideation, behavior, attempt); tension; rare: aggression; self-injurious behavior; mania

Renal and urinary disorder: frequent: dysuria; pollakiuria; urinary retention; infrequent: hematuria; rare: proteinuria

Reproductive system and breast disorders: rare: postmenopausal hemorrhage

Respiratory, thoracic and mediastinal disorders: infrequent: epistaxis; yawning

Skin and subcutaneous tissue disorders: frequent: rash; infrequent: dry skin; pruritus; urticaria; increased tendency to bruise

Vascular disorders: frequent: orthostatic hypotension; infrequent: hypotension; rare: orthostatic hypertension

Weight

In short-term clinical studies, levomilnacipran extended release capsules-treated patients experienced a mean weight loss of 0.59 kg compared to a gain of 0.02 kg for placebo-

treated patients. The proportion of patients with a weight gain > 7% was 0.6% in the levomilnacipran extended release capsules group and 0.9% in the placebo group. No dose-related weight changes were observed. Results from a one-year open-label study were consistent with the findings from the placebo-controlled studies.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Slight elevations of liver enzyme levels (ALT, AST, and ALP) were noted among levomilnacipran extended release capsules-treated patients in clinical studies. Mean increases (U/L) across all studies ranged from 2.1 to 2.7 for ALT, from 1.1 to 2.3 for AST, and from 1.9 to 3.6 for ALP. Few levomilnacipran extended release capsules-treated patients experienced potentially clinically significant (PCS) criteria for ALT (0.7%), compared to placebo (0.1%). While a few patients were discontinued due to changes in liver function parameters, other patients with elevations continued on levomilnacipran extended release capsules with enzyme levels returning to normal during on-going treatment. No patient had concurrent PCS elevations in ALT or AST and total bilirubin.

8.5 Post-Market Adverse Reactions

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

The following adverse reaction has been identified during post-approval use of levomilnacipran extended release capsules or other selective serotonin and norepinephrine reuptake inhibitors. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac disorders: Takotsubo cardiomyopathy

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions
• Monoamine Oxidase Inhibitors (MAOIs): See 2 CONTRAINDICATIONS and 9.4 Drug-Drug Interactions- Monoamine Oxidase Inhibitors (MAOIs)

9.2 Drug Interactions Overview

In vitro and *in vivo* studies showed that levomilnacipran extended release capsules has low potential to be involved in clinically significant pharmacokinetic drug interactions.

9.3 Drug-Behavioural Interactions

Alcohol

As with other psychotropic medications, the use of alcohol by patients taking APO-LEVOMILNACIPRAN is not recommended.

9.4 Drug-Drug Interactions

Monoamine Oxidase Inhibitors (MAOIs)

APO-LEVOMILNACIPRAN is contraindicated in patients taking MAOIs, or within at least 14 days of discontinuation. See 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, Serotonin toxicity / serotonin syndrome and 4.1 Dosing Considerations.

Serotonergic Drugs

Based on the known mechanism of action of levomilnacipran and the potential for serotonin toxicity, also known as serotonin syndrome, caution is advised when APO-LEVOMILNACIPRAN is coadministered with other drugs that may affect the serotonergic neurotransmitter systems (e.g., SSRIs, SNRIs, tryptophan, triptans, fentanyl and its analogues, dextromethorphan, tramadol, tapentadol, meperidine, methadone and pentazocine). See 7 WARNINGS AND PRECAUTIONS, Serotonin toxicity / serotonin syndrome.

Drug that Increase Heart Rate and/or Blood Pressure

Levomilnacipran extended release capsules increase heart rate and blood pressure. Levomilnacipran extended release capsules may exacerbate the hemodynamic effects of other drugs that also increase heart rate and/or blood pressure (e.g., sympathomimetics).

Central Nervous System (CNS) Active Agents

The risk of using levomilnacipran extended release capsules in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised when APO-LEVOMILNACIPRAN is prescribed in combination with other CNS-active drugs.

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 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 and SNRIs are co-administered with warfarin. Patients receiving warfarin therapy should be carefully monitored when APO-

LEVOMILNACIPRAN is initiated or discontinued. See 7 WARNINGS AND PRECAUTIONS, Hematologic.

Potential for Other Drugs to Affect APO-LEVOMILNACIPRAN

Table 6 - Summary of Effect of Co-administered Drugs on Exposure to Levomilnacipran

Co-administered drug	Source of Evidence	Effect	Clinical comment
Ketoconazole (potent CYP3A4 inhibitor)	CT	Increased levomilnacipran plasma exposure (C_{max} by 39% and AUC by 57%)	Concomitant use of APO-LEVOMILNACIPRAN with potent inhibitors of CYP3A4 may result in higher concentrations of levomilnacipran extended release capsules.
Carbamazepine (CYP3A4 inducer)	CT	Reduced levomilnacipran plasma exposure (C_{max} by 26% and AUC by 29%)	No dosing adjustment is recommended when APO-LEVOMILNACIPRAN is co-administered with inducers of CYP3A4.
Alprazolam (substrate of CYP3A4)	CT	No significant effect on levomilnacipran plasma exposure	No dosing adjustment is recommended when APO-LEVOMILNACIPRAN is co-administered with substrates of CYP3A4.
Inhibitors of CYP2C8, CYP2C19, CYP2D6 and CYP2J2	*In vitro*	Not expected to significantly alter plasma concentrations of levomilnacipran	*In vitro* studies have shown that these isoenzymes have minimal contributions to metabolism of levomilnacipran.
Alcohol	*In vitro*	Increased release of levomilnacipran at 2 hours by approximately 9.5%. 23 % and 56% in the	No *in vivo* study has been conducted for the effect of alcohol on drug exposure.

Co-administered drug	Source of Evidence	Effect	Clinical comment
		presence of 5%, 20% and 40% (v/v) alcohol respectively. Effect of 40% alcohol resulted in nearly complete drug release in 4 hours rather than a controlled release over 24 hours.	Concomitant use of APO-LEVOMILNACIPRAN and alcohol is not recommended.
Legend: CT = Clinical Trial			

Potential for APO-LEVOMILNACIPRAN to Affect Other Drugs

Table 7 - Summary of Effect of Levomilnacipran extended release capsules on Exposure to Co-administered Drugs

Co-administered drug	Source of Evidence	Effect	Clinical comment
Alprazolam, carbamazepine (substrates of CYP3A4)	*in vitro*	Levomilnacipran slightly inhibits CYP3A4	No dosing adjustment recommended
	CT	No significant effect on alprazolam or carbamazepine exposure	
Substrates of CYP2C9	*In vitro*	Levomilnacipran slightly inhibits CYP2C9	No dosing adjustment is recommended when APO-LEVOMILNACIPRAN is co-administered with substrates of CYP2C9.
Substrates of CYP1A2, CYP2A6, CYP2C8, CYP2C19, CYP2D6, and CYP2E1	*In vitro*	No significant effect	No dosing adjustment is recommended when APO-LEVOMILNACIPRAN is co-administered with substrates of CYP1A2, CYP2A6, CYP2C8, CYP2C19, CYP2D6 or CYP2E1.

Co-administered drug	Source of Evidence	Effect	Clinical comment
Membrane Transporters	*In vitro*	No significant effect	*In vitro* evaluations indicated that levomilnacipran does not significantly interact with P-glycoprotein, BCRP, OATP1B1, OATP1B3, OAT1, OAT3 or OCT2.
Drugs Highly Bound to Plasma Protein	T	Interaction unlikely	Because levomilnacipran has low protein binding (22%), it is unlikely to interact with highly protein bound drugs.
Legend: CT = Clinical Trial; T = Theoretical			

9.5 Drug-Food Interactions

Food has no clinically meaningful effect on the bioavailability of levomilnacipran. APO-LEVOMILNACIPRAN may be taken with or without food. However, tolerability was improved when taken with food particularly with respect to gastrointestinal adverse events (vomiting and nausea were markedly reduced).

9.6 Drug-Herb Interactions

In common with other SSRIs and SNRIs, pharmacodynamic interactions between levomilnacipran extended release capsules and the herbal remedy St. John's Wort may occur and may result in an increase in undesirable effects. Interactions with other herbs 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

Levomilnacipran is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI). The exact mechanism of the antidepressant effect of levomilnacipran is unknown but is thought to be related to the potentiation of these neurotransmitters in the central nervous system.

10.2 Pharmacodynamics

Nonclinical studies have shown that levomilnacipran binds with high affinity to the norepinephrine (NE) and serotonin (5-HT) transporters (K_i = 71 to 91 nM and 11 nM respectively at human transporters). Levomilnacipran inhibits the uptake of both NE and 5-HT *in vitro* and *in vivo*; preferentially inhibiting reuptake of NE over 5-HT by approximately 2-fold. Levomilnacipran does not directly affect the uptake of dopamine or other neurotransmitters.

Levomilnacipran has no significant affinity for serotonergic (5-HT1 to 7), α- and β-adrenergic, muscarinic (M1 to 5), histamine (H1 to 4), dopamine (D1 to 5), opiate, benzodiazepine, and γ-aminobutyric acid (GABA) receptors *in vitro*.

Levomilnacipran has no significant affinity for Ca^{++}, K^+, Na^+ and Cl^- channels and does not inhibit the activity of human monoamine oxidases (MAO-A and MAO-B) or acetylcholinesterase.

Cardiac Electrophysiology and Hemodynamics

Levomilnacipran at 120 mg daily (maximum therapeutic dose) and 300 mg daily (supratherapeutic dose) was evaluated in a randomized, placebo-, and active-controlled (moxifloxacin 400 mg), parallel group, thorough ECG study in 170 healthy subjects. Subjects randomized to levomilnacipran treatment received escalating once-daily doses on Day 1 to Day 24. Serial ECG data were collected on Day -2 (baseline), Day 11 (120 mg dose) and Day 24 (300 mg dose) at predose, and 1, 2, 3, 4, 6, 8, 12, 16, 20, and 23 hours postdose.

No clinically significant changes in QTcF interval ($QTcF = QT/RR^{0.33}$) were noted in this study.

Levomilnacipran caused an increase in heart rate. The mean change from baseline in heart rate in the levomilnacipran treatment group on Day 11 (120 mg dose) was significantly greater than the placebo group at multiple timepoints, ranging from 15 to 20 bpm with a maximum mean difference from placebo of 20.2 bpm (90% CI 18.0, 22.4) at 6 h. The effect was somewhat greater in the levomilnacipran treatment group on Day 24 (300 mg dose), with mean differences in heart rate ranging from 19 to 22 bpm with a maximum mean difference from placebo of 22.1 bpm (90% CI 19.8, 24.3) at 6 h.

On Day 11, the proportion of subjects with heart rate values >90 bpm at any recorded timepoint was 2.7% with placebo and 50.6% with levomilnacipran (120 mg dose). On Day 24, the corresponding values were 2.8% with placebo and 60.0% with levomilnacipran (300 mg dose).

None of the placebo-treated subjects had heart rate values >100 bpm on Days 11 or 24; however, heart rate values >100 bpm at any recorded timepoint were observed in 20.2% of subjects receiving levomilnacipran 120 mg on Day 11 and 26.3% receiving levomilnacipran 300 mg on Day 24.

Blood pressure in this thorough ECG study was measured using automatic blood pressure monitors at baseline (one measurement), and at predose, and 2, 3, 6, 8, and 24 hours postdose on Days 11 (120 mg dose), and 24 (300 mg dose). Levomilnacipran showed increases in blood pressure from baseline at recorded time points on Days 11 and 24.

As shown in **Table 8**, the difference from placebo in SBP ranged from 3.8 to 7.2 mmHg for levomilnacipran (120 mg dose) on Day 11. The mean difference from placebo in SBP ranged from 5.4 to 7.9 mmHg for levomilnacipran (300 mg dose) on Day 24.

The mean difference from placebo in DBP ranged from 6.1 to 8.1 mmHg for levomilnacipran (120 mg dose) on Day 11. The mean difference from placebo in DBP ranged from 7.9 to 10.6 mmHg for levomilnacipran (300 mg dose) on Day 24.

Table 8 - Change from Baseline in Blood Pressure

Day Time	Systolic BP (mmHg) Mean Change from Baseline (90% CI)			Diastolic BP (mmHg) Mean Change from Baseline (90% CI)		
	Placebo	LVM[a]	Difference	Placebo	LVM[a]	Difference
Day 11						
Predose	-3.6 (-5.0, -2.2)	1.4 (0.1, 2.7)	5.0[b] (3.0, 6.9)	-3.9 (-5.1, -2.7)	2.2 (1.1, 3.3)	6.1[b] (4.5, 7.7)
2.0	-4.6 (-6.0, -3.2)	-0.1 (-1.4, 1.2)	4.5[b] (2.6, 6.4)	-3.6 (-4.8, -2.3)	3.8 (2.7, 4.9)	7.3[b] (5.7, 9.0)
3.0	-5.9 (-7.4, -4.5)	0.3 (-1.0, 1.6)	6.2[b] (4.3, 8.1)	-3.2 (-4.4, -2.0)	3.9 (2.8, 5.0)	7.1[b] (5.4, 8.7)
6.0	-1.5 (-3.0, -0.1)	2.2 (1.0, 3.5)	3.8[c] (1.9, 5.7)	-4.2 (-5.4, -3.0)	2.5 (1.4, 3.6)	6.7[b] (5.1, 8.4)
8.0	-4.9 (-6.4, -3.5)	-0.0 (-1.3, 1.3)	4.9[b] (3.0, 6.8)	-5.6 (-6.8, -4.4)	2.1 (1.0, 3.2)	7.8[b] (6.1, 9.4)
24.0	-5.4 (-6.8, -3.9)	1.8 (0.5, 3.1)	7.2[b] (5.2, 9.1)	-5.3 (-6.5, -4.1)	2.7 (1.6, 3.8)	8.1[b] (6.4, 9.7)
Day 24						
Predose	-3.9 (-5.4, -2.5)	2.5 (1.2, 3.9)	6.5[b] (4.5, 8.4)	-3.7 (-5.0, -2.5)	4.1 (3.0, 5.3)	7.9[b] (6.2, 9.5)
2.0	-5.9 (-7.3, -4.4)	0.9 (-0.5, 2.2)	6.7[b] (4.7, 8.7)	-3.7 (-4.9, -2.5)	5.3 (4.1, 6.4)	8.9[b] (7.3, 10.6)
3.0	-6.6 (-8.1, -5.2)	1.3 (-0.1, 2.6)	7.9[b] (5.9, 9.9)	-3.9 (-5.2, -2.7)	6.7 (5.5, 7.8)	10.6[b] (8.9, 12.3)
6.0	-3.8 (-5.3, -2.4)	1.6 (0.2, 2.9)	5.4[b] (3.4, 7.4)	-4.8 (-6.1, -3.6)	4.1 (2.9, 5.2)	8.9[b] (7.2, 10.6)
8.0	-6.1 (-7.5, -4.6)	0.3 (-1.1, 1.6)	6.4[b] (4.4, 8.3)	-4.3 (-5.6, -3.1)	4.4 (3.3, 5.6)	8.8[b] (7.1, 10.4)
24.0	-6.0 (-7.5, -4.6)	0.7 (-0.7, 2.0)	6.7[b] (4.7, 8.7)	-4.4 (-5.7, -3.2)	4.2 (3.1, 5.4)	8.7[b] (7.0, 10.3)

[a] Levomilnacipran subjects were receiving 120 mg dose on Day 11 and 300 mg dose on Day 24
[b] $p \leq 0.0001$
[c] $p < 0.01$
LVM = levomilnacipran; CI = Confidence Intervals

10.3 Pharmacokinetics

Following an oral administration, the mean apparent total clearance of levomilnacipran is 21 to 29 L/h and the apparent volume of distribution is 387 to 473 L. The pharmacokinetics of levomilnacipran (25 to 300 mg once daily) are dose-proportional. Steady-state concentrations of levomilnacipran are predictable from single-dose data. Elimination of levomilnacipran is predominantly by renal excretion with a terminal elimination half-life of approximately 12 hours. After daily dosing of levomilnacipran extended release capsules 120 mg, the mean C_{max} value is 341 ng/mL, and the mean steady-state AUC value is 5196 ng·h/mL. Interconversion between levomilnacipran and its stereoisomer does not occur in humans.

Absorption

Peak concentration of levomilnacipran is reached at a median of 6 to 8 hours (T_{max}) after oral administration. The absolute oral bioavailability of levomilnacipran is >80% and is not affected by food.

Distribution

Levomilnacipran is widely distributed with an apparent volume of distribution of 387 to 473 L; plasma protein binding is 22%.

Metabolism

Levomilnacipran undergoes desethylation to form desethyl levomilnacipran and hydroxylation to form p-hydroxy-levomilnacipran. Both oxidative metabolites undergo further conjugation with glucuronide to form conjugates. The desethylation is catalyzed primarily by CYP3A4 with minor contribution by CYP2C8, 2C19, 2D6, and 2J2. In human studies, ketoconazole, a potent inhibitor of CYP3A4, and carbamazepine, a potent inducer of CYP3A4, did not result in clinically significant drug-drug interactions when administered with levomilnacipran. See 9.4 Drug-Drug Interactions.

Elimination

Levomilnacipran and its metabolites are eliminated primarily by renal excretion. Following oral administration of ^{14}C-levomilnacipran solution, approximately 58% of the dose is excreted in urine as unchanged levomilnacipran. N-desethyl levomilnacipran is the major metabolite excreted in the urine and accounted for approximately 18% of the dose. Other identifiable metabolites excreted in the urine are levomilnacipran glucuronide (4%), desethyl levomilnacipran glucuronide (3%), p-hydroxy levomilnacipran glucuronide (1%), and p-hydroxy levomilnacipran (1%). The metabolites are inactive.

Special Populations and Conditions

- **Pediatrics:** Based on the data submitted and reviewed by Health Canada, the safety and efficacy of levomilnacipran extended release capsules in pediatric patients has not been established; therefore Health Canada has not authorized an indication for pediatric use. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, 7 WARNINGS AND PRECAUTIONS, Potential association with behavioural and emotional changes, including self-harm and 7.1.3 Pediatrics.

- **Geriatrics:** No dose adjustment is recommended on the basis of age. In a multiple-dose clinical pharmacokinetic study, elderly subjects (> 65 years) had a slightly higher exposure (C_{max} by 24% and AUC by 26%) of levomilnacipran than younger subjects (18 to 45 years).

- **Sex**: The systemic exposure in females is slightly higher (C_{max} by 17% and AUC by 14%) than that in males; however, no dose adjustment is necessary.

- **Hepatic Insufficiency:** Hepatic elimination of levomilnacipran is low. In mild, moderate, and severe hepatic impairment, no dose adjustment is necessary.

  The presence of mild (Child-Pugh A), moderate (Child-Pugh B), or severe (Child-Pugh C) hepatic impairment increased the apparent clearance of levomilnacipran by 7%, and decreased by 8% and 25%, respectively, without significant change in terminal elimination half-life.

- **Renal Insufficiency**: Renal excretion plays a predominant role in the elimination of levomilnacipran. In mild (creatinine clearance of 50 to 79 mL/min), moderate (creatinine clearance of 30 to 49 mL/min), or severe (creatinine clearance <30 mL/min) renal impairment, AUC increased by 23%, 93%, or 180%, respectively, the apparent clearance of levomilnacipran decreased by 19%, 49%, or 64%, respectively and terminal elimination half-life increased by 28%, 43%, or 105%, respectively, relative to healthy subjects with normal renal function. Dosing adjustment is necessary for patients with moderate or severe renal impairment. See 4.2 Recommended Dose and Dosage Adjustment, Dosing in Special Populations and Conditions.

11 STORAGE, STABILITY AND DISPOSAL

APO-LEVOMILNACIPRAN should be stored at room temperature 15°C to 30°C.

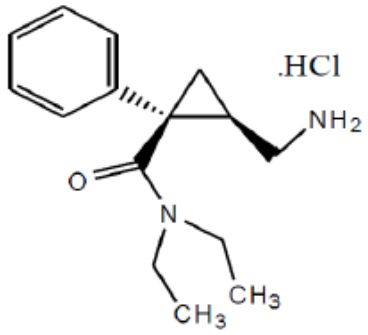
12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Non-proprietary name:	Levomilnacipran hydrochloride
Chemical name:	(1S,2R)-2-(Aminomethyl)-N,N-diethyl-1-phenylcyclopropanecarboxamide hydrochloride
Molecular formula and molecular mass:	$C_{15}H_{22}N_2O \cdot HCl$ and 282.81 g/mol
Structural formula:	
Physicochemical properties:	Levomilnacipran hydrochloride is a white to off-white crystalline powder that is freely soluble in methanol, water and ethanol insoluble in cyclohexane.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Major Depressive Disorder

Table 9 - Summary of patient demographics for clinical studies supporting efficacy of levomilnacipran extended release capsules in the Treatment of Major Depressive Disorder

Study	Trial Design	Oral Dosage	Number of Study Subjects (N) [Male/Female (M/F)]	Mean Age (Range)	Mean Baseline MADRS Score
LVM-MD-01	8-week, multicentre, randomized, double-blind, placebo-controlled, parallel-group, fixed dose study	levomilnacipran 40 mg, 80 mg or 120 mg once daily or placebo	N=713 40 mg: n=178 80 mg: n=179 120 mg: n=180 placebo: n=176 [266M/447F]	41 (18-65)	36
LVM-MD-10	8-week, multicentre, randomized, double-blind, placebo-controlled, parallel-group, fixed dose study	levomilnacipran 40 mg or 80 mg once daily or placebo	N=562 40 mg: n=188 80 mg: n=188 placebo: n=186 [205M/357F]	43 (18-74)	31
LVM-MD-02	8-week, multicentre, randomized, double-blind, placebo-controlled, parallel-group flexible dose study	levomilnacipran 40 mg to 120 mg once daily or placebo	N=357 40-120 mg: n=175 placebo: n=182 [142M/215F]	43 (19-78)	36
LVM-MD-03	8-week, multicentre, randomized, double-blind, placebo-controlled, parallel-group	levomilnacipran 40 mg to 120 mg once daily or placebo	N=434 40-120 mg: n=217 placebo: n=217 [151M/283F]	45 (18-76)	35

Study	Trial Design	Oral Dosage	Number of Study Subjects (N) [Male/Female (M/F)]	Mean Age (Range)	Mean Baseline MADRS Score
	flexible dose study				

The efficacy of levomilnacipran extended release capsules for the treatment of major depressive disorder (MDD) was studied in four 8-week randomized, double-blind, placebo-controlled studies (at doses of 40 to 120 mg once daily) in adult (18 to 78 years of age) outpatients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for MDD. Of the total number of levomilnacipran extended release capsules-treated subjects in short-term clinical studies, only 2.8% of patients were 65 or older. Two of the studies were fixed dose (Study LVM-MD-01 and Study LVM-MD-10) and two were flexible dose (Study LVM-MD-02 and Study LVM-MD-03). The designs of the studies are summarized in **Table 9.**

The primary efficacy endpoint in all studies was mean change from baseline to Week 8-endpoint on the Montgomery Asberg Depression Rating Scale (MADRS). All studies included a 1-week single-blind placebo lead-in period, followed by an 8-week, double-blind treatment period.

In three of the four studies (LVM-MD-01, LVM-MD-10, and LVM-MD-03), levomilnacipran extended release capsules demonstrated statistical superiority over placebo in the improvement of depressive symptoms as measured by the mean change from baseline to Week 8 in the MADRS total score (see **Table 10**).

Table 10 - Summary of the Least Square Mean Difference from Placebo in Change from Baseline for MADRS Score, in Placebo-Controlled Studies for Major Depressive Disorder (ITT Population)

Study	Levomilnacipran extended release capsules			
	40 mg	80 mg	120 mg	40-120 mg
LVM-MD-01 (fixed-dose) **LSMD** **95% CI** **p-value**	 -3.23 (-5.92, -0.54) 0.0186	 -3.99 (-6.69, -1.29) 0.0038	 -4.86 (-7.59, -2.12) 0.0005	 NA
LVM-MD-10 (fixed-dose) **LSMD** **95% CI** **p-value**	 -3.30 (-5.46, -1.15) 0.0027	 -3.14 (-5.29, -0.99) 0.0043	 NA	 NA
LVM-MD-03 (flexible-dose) **LSMD**	NA	NA	NA	-3.1 (-5.26, -0.94) 0.0051

Study	Levomilnacipran extended release capsules			
	40 mg	80 mg	120 mg	40-120 mg
95% CI p-value				
LSMD = Least Squares Mean Difference; CI = Confidence Interval; NA = Not applicable				

Results from subgroup analyses by gender were not consistent across the pivotal trials; however, clinical studies with levomilnacipran extended release capsules were not designed with adequate power to detect a gender difference. Both fixed-dose trials showed better response to treatment in male subjects. Females in these studies either had a reduced treatment response at doses above 40 mg/day compared to males (Study LVM-MD-01) or failed to demonstrate clinically significant improvements in study outcomes over placebo (Study LVM-MD-10). Female subjects, however, outperformed male subjects in the positive flexible-dose study (Study LVM-MD-03).

Fixed-dose studies failed to demonstrate a clear dose-response relationship for either male or female subjects.

The key secondary instrument was the Sheehan Disability Scale (SDS), a validated scale that measures the extent emotional symptoms disrupt patients functioning in 3 life domains: (work/school, social life and family life).

Levomilnacipran extended release capsules demonstrated superiority over placebo in functional improvement as measured by mean change from baseline to Week 8 in the SDS total score in studies LVM-MD-01, LVM-MD-10 and LVM-MD-03.

Additional efficacy parameters in the studies included HAMD-17 (17 item Hamilton Rating Scale for Depression), CGI-S (Clinical Global Impressions - Severity Scale) and MADRS-CR (Montgomery-Åsberg Depression Rating Scale - Clinician Rated) response and remission rates. In addition CGI-I (Clinical Global Impressions - Improvement Scale) was assessed in studies LVM-MD-01 and LVM-MD-03 and MEI-SF (Motivation and Energy Inventory - Short Form) was assessed in Study LVM-MD-03. Results of the additional efficacy parameters were generally supportive of the primary efficacy result.

Maintenance Study

The efficacy of levomilnacipran extended release capsules for the maintenance treatment of MDD was demonstrated in a multicenter, randomized, double-blind, placebo-controlled trial of adult patients meeting DSM-V criteria for MDD (baseline MADRS total score of 32.2). Patients received flexible dose titration of levomilnacipran extended release capsules (40 mg, 80 mg, or 120 mg/day) during the first 8 weeks (run-in phase) of an open-label treatment phase (OLTP), responders were eligible to enter a 12-week, open-label, fixed-dose stabilization phase (SP). Three hundred twenty-four (324) patients who met the response criteria (MADRS of 12 or less) after 20 weeks of open-label treatment were randomized to the double-blind treatment phase (DBTP) (baseline mean MADRS total score of 4.7) for 26 weeks. The primary efficacy endpoint was the time to first relapse during the DBTP, defined as the number of days from the randomization date to the relapse date.

Recurrence of depressive episode was defined as a MADRS total score ≥ 18 at 2 consecutive visits or insufficient therapeutic response as judged by the investigator. Patients on levomilnacipran extended release capsules experienced a statistically significantly longer time to have recurrence of depressive episodes than did patients on placebo. In the placebo group 39 of 159 patients experienced relapse (24.5%) while 24 of 165 levomilnacipran extended release capsules-treated patients experienced relapse (14.5%).

14.2 Comparative Bioavailability Studies

Fasting Study

A double-blinded, randomized, single-dose, two-way, crossover, comparative bioavailability study of APO-LEVOMILNACIPRAN extended release capsules 120 mg (Apotex Inc.) and FETZIMA® extended release capsules 120 mg (Allergan Inc.) administered as a single oral dose (1 x 120 mg capsule) was conducted in healthy, adult, male subjects under fasting conditions.

Comparative bioavailability data from 16 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOVAILABILITY DATA

Levomilnacipran (1 x 120 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng·h/mL)	6261.17 6398.21 (17.38)	5976.59 6189.56 (25.14)	104.8	95.0 – 115.6
AUC_I (ng·h/mL)	6374.10 6515.49 (17.54)	6095.11 6321.25 (26.02)	104.6	94.5 – 115.8
C_{max} (ng/mL)	306.07 312.22 (16.92)	283.23 289.68 (19.58)	108.1	97.1 – 120.3
T_{max}[3] (h)	6.00 (4.50 – 11.00)	6.25 (4.50 – 8.00)		
$T_{1/2}$[4] (h)	11.64 (14.14)	11.66 (17.99)		

[1] APO-LEVOMILNACIPRAN (as levomilnacipran hydrochloride) extended release capsules, 120 mg (Apotex Inc.)
[2] FETZIMA® (levomilnacipran as levomilnacipran hydrochloride) extended release capsules, 120 mg (Allergan Inc.) were purchased in Canada.
[3] Expressed as median (range) only.
[4] Expressed as arithmetic mean (CV%) only.

Fed Study

A double-blinded, randomized, single-dose, two-way, crossover, comparative bioavailability study of APO-LEVOMILNACIPRAN extended release capsules 120 mg (Apotex Inc.) and FETZIMA® extended release capsules 120 mg (Allergan Inc.) administered as a single oral dose (1 x 120 mg capsule) was conducted in healthy, adult, male subjects under high-fat, high-calorie fed conditions.

Comparative bioavailability data from 24 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOVAILABILITY DATA

Levomilnacipran (1 x 120 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng·h/mL)	7100.06 7513.53 (25.37)	6562.87 6826.62 (25.36)	108.2	95.0 – 123.2
AUC_I (ng·h/mL)	7261.29 7681.91 (25.63)	6730.18 7003.26 (25.94)	107.9	95.0 – 122.5
C_{max} (ng/mL)	340.99 358.61 (23.62)	292.17 303.20 (23.74)	116.7	102.5 – 132.8
T_{max}[3] (h)	6.50 (5.00 – 12.00)	6.50 (4.50 – 11.00)		
$T_{1/2}$[4] (h)	12.09 (13.96)	12.43 (15.03)		

[1] APO-LEVOMILNACIPRAN (as levomilnacipran hydrochloride) extended release capsules, 120 mg (Apotex Inc.)
[2] FETZIMA® (levomilnacipran as levomilnacipran hydrochloride) extended release capsules 120 mg (Allergan Inc.) were purchased in Canada.
[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

Safety Pharmacology Studies

Levomilnacipran was studied in a core battery of acute, nonclinical safety pharmacology studies to determine the effects on CNS, respiratory, and cardiovascular function. Acute, nonclinical safety findings are described as follows:

- The effect of levomilnacipran on hERG K+ currents was studied *in vitro* in CHO-K1 cells stably expressing the hERG channel. Levomilnacipran (0.001, 0.01, 0.1, 1, and 10 mcM) produced a concentration-dependent inhibition of the maximum tail current amplitude, with an estimated IC50 > 10 mcM.
- The effect of levomilnacipran (0.01, 0.1, 1, and 10 mcM) on cardiac action potential physiology was assessed *in vitro* in canine Purkinje fiber preparations at both a normal stimulation rate (1 Hz) and a low stimulation rate (0.33 Hz). Levomilnacipran did not significantly affect the cardiac action potential parameters measured at any concentration tested with normal stimulation rate (1 Hz). When tested using the low stimulation rate (0.33 Hz), levomilnacipran produced a statistically significant increase in APD90 (+19 msec; $p < 0.05$) at a concentration of 1 mcM and in both APD70 (+22 msec; $p < 0.01$) and ADP90 (+37 msec; $p < 0.01$) at 10 mcM compared with the vehicle control.
- Levomilnacipran was also evaluated in conscious telemetry female Beagle dogs. Animals received oral administration of levomilnacipran (10 mg/kg/day) for 5 days in three series of experiments with a 4-day washout period. Cardiovascular measurements (blood pressure, heart rate, ECG) were noted 3 days before the beginning of test article administration, following a single dose (Day 1), and after 5 days of dosing. Levomilnacipran produced a significant increase in heart rate and diastolic blood pressure after both a single dose and after 5 days of dosing compared with the vehicle control.
- The effect of single oral doses of levomilnacipran on cardiovascular function was assessed *in vivo* in conscious cynomolgus monkeys. Cardiovascular function (arterial blood pressure, heart rate, ECG) was monitored by telemetry for 2 h before test substance administration and for 24 h after test substance administration. Levomilnacipran 5 and 15 mg/kg did not significantly affect the QT or QTc intervals or the QRS complex throughout the testing period, but levomilnacipran 45 mg/kg produced a significant increase in the QT (up to 48 msec from pretest) and QTc (up to 57 and 55 msec from pretest when corrected with Bazett's and Fridericia's formula, respectively) intervals. In addition, there was a small increase in the QRS complex duration (up to 6 msec from pretest) for up to 6 h after levomilnacipran administration. When compared with the vehicle group, levomilnacipran (5, 15, and 45 mg/kg) produced moderate, but statistically significant increases in arterial blood pressure (mean, systolic, diastolic), with the maximum increase at 30 min after levomilnacipran administration and returning to predose levels by 4 h. The increase in arterial blood pressure (about 15 to 21 mmHg from pretest) was not dose related. There were no clear drug-related changes in heart rate at doses of levomilnacipran up to 45 mg/kg. Compared to the 120 mg human dose, oral administration of 45 mg/kg levomilnacipran in monkeys produced >20-fold higher drug levels in the plasma.
- At therapeutically relevant concentrations, levomilnacipran is not expected to have an effect on respiratory function, but at concentrations ~26-fold greater than the 120 mg clinical dose, levomilnacipran increases respiratory rate, decreases peak inspiratory flow, decreases inspiration time, decreases expiration time, decreases tidal volume, decreases minute volume, and increases airway resistance index in rat.

- Levomilnacipran decreases motor activity and body temperature in rats at all doses tested after a single oral dose. At high doses (6- to 66- fold the plasma concentration of the 120 mg clinical dose), levomilnacipran also decreases arousal, alters posture and gait and induces palpebral ptosis.

General Toxicology:

The principal toxicology studies included single-dose and repeat-dose studies in rats and monkeys; genetic toxicology studies; 2-year carcinogenicity studies in transgenic mice and rats; and reproductive and developmental toxicology studies in rats and rabbits.

Single-Dose

The toxicological potential of levomilnacipran following single-dose (acute) oral administration was evaluated in rats and mice. Clinical signs of acute toxicity consisted primarily of tremors and convulsions. The approximate lethal dose was determined to be 140 mg/kg in mice and < 215 mg/kg in rats.

Repeat-Dose

The toxicological potential of levomilnacipran was evaluated in rats and monkeys for up to 6 months or 12 months, respectively.

Rats

In a 4-week toxicity study, rats were administered 0, 10, 35 or 120 mg/kg/day and the no-observed adverse -effect level (NOAEL) was 10 mg/kg/day based on decreases in body weight and food consumption and treatment-related centrilobular hepatocellular hypertrophy. In a 13-week toxicity study, rats were administered 0, 10, 35 or 120 mg/kg/day and based on centrilobular hepatocellular hypertrophy the NOAEL was determined to be 10 mg/kg/day a dose which represents an animal-to human exposure margin of 0.4-fold relative to the human exposure from 120 mg/day of levomilnacipran. Following 6-months of dose administration at 0, 10, 30 or 120 (males) or 100 (females) mg/kg/day the NOAEL was determined to be 30 mg/kg/day for males and 100 mg/kg/day for females based on decreased activity, body weight and food consumption and increases in urine volume and liver weight with correlated minimal to mild centrilobular hepatocellular hypertrophy. The NOAELs represent animal-to-human exposure margins of 2-fold (male) and 14-fold (female) relative to the human exposure from 120 mg/day of levomilnacipran.

Monkeys

The toxicological potential of levomilnacipran following repeat-dose oral administration for 13 weeks and 12 months was evaluated in cynomolgus monkeys at doses up to 45 mg/kg/day via direct dose or 90 mg/kg/day via dose escalation.

In a 13-week toxicity study, monkeys were administered 0, 5, 15, or 45 mg/kg/day; reversible decreases in body weight and food consumption were noted and the NOAEL was 15 mg/kg/day a dose which represents an animal-to-human exposure margin of 2-fold relative to the human exposure from 120 mg/day of levomilnacipran. In a 12-month toxicity study, monkeys were administered levomilnacipran via dose escalation at 0, 5/10, 15/30 or

45/70/90 mg/kg/day. All escalations were completed within two weeks of dose initiation. The NOAEL was determined to be 15/30 mg/kg/day based on emesis, decreases in activity, changes in clinical chemistry parameters (decreased albumin, albumin:globulin, cholesterol and increased GGT and ALT), and increased liver weights with correlates of minimal panlobular hepatocellular hypertrophy and minimal to mild midzonal vacuolation of hepatocytes. The NOAEL represents an animal-to-human exposure margin of 8-fold relative to the human exposure from 120 mg/day of levomilnacipran.

Genotoxicity:

Levomilnacipran was not mutagenic when evaluated *in vitro* in a bacterial mutagenicity study (Ames test) and not genotoxic in a mouse lymphoma study. It was not clastogenic in an *in vivo* micronucleus assay in rats.

Carcinogenicity:

The carcinogenic potential of levomilnacipran was evaluated in a 6-month carcinogenicity study in transgenic Tg.rasH2 mice and in a 2-year carcinogenicity study in rats.

Mice

In a 6-month carcinogenicity study, Tg.rasH2 transgenic mice were administered 0, 15, 50, 150 mg/kg/day levomilnacipran daily via oral gavage. With the exception of a small increase in splenic hemangiosarcoma in males which received 150 mg/kg/day (the highest dose tested) there was no increase in incidence of neoplastic lesions due to levomilnacipran. Splenic hemangiosarcomas are one of the most common spontaneous tumor types in the Tg.rasH2 transgenic mouse. Although the incidence observed in this study was slightly beyond the facility historical control values, it is comparable to the spontaneous incidences reported in the literature for this strain of transgenic mouse. In addition, since this slight numerical increase of a common spontaneous tumor occurred in only one gender in this study, and taken together with other assessments of the carcinogenic/mutagenic potential of levomilnacipran, the results are not regarded to represent a biologically-significant signal that would be meaningful for the purposes of carcinogenic risk assessment.

Rats

In a 2-year carcinogenicity study, rats were administered 0, 10, 30, or 90 mg/kg/day levomilnacipran daily via oral gavage. Survival incidence was similar across treatment groups and no increase in neoplastic lesions was noted, indicating that levomilnacipran is not carcinogenic.

Reproductive and Developmental Toxicology:

Impairment of Fertility

The potential effects of levomilnacipran on gonadal function, mating behavior, reproductive performance and early pregnancy were evaluated in rats at oral doses of 0, 10, 30, or 100 mg/kg/day. The NOAEL was 100 mg/kg/day based on reductions in body weight gain and food consumption. There were no levomilnacipran effects on male and female fertility parameters.

Teratogenic Effects

The potential effects of levomilnacipran on embryo/fetal development were evaluated in rats and rabbits at oral doses on 0, 10, 30 or 100 mg/kg/day.

In the rat and rabbit embryo/fetal development studies, decreases in maternal body weight gain and food consumption were noted. In the fetuses, increases in the incidence of ossification anomalies were noted but were of no toxicological significance. In both species, the NOAEL was determined to be 100 mg/kg/day, a dose which represents a rat or rabbit animal-to-human exposure margin of 9-fold and 4-fold, respectively relative to the human exposure from 120 mg/day of levomilnacipran.

When levomilnacipran was administered to pregnant rats at an oral dose of 60 mg/kg/day, 5 times the MRHD, during organogenesis and throughout pregnancy and lactation, there was an increase in early postnatal pup mortality; no pup mortality was seen at 20 mg/kg/day, 1.6 times the MRHD on a mg/m^2 basis. Among the surviving pups, pre- and post-weaning pup weight gain was reduced up to at least 8 weeks of age; however, physical and functional development, including reproductive performance of the progeny, was not affected. The effects on body weight gain were not seen at 7 mg/kg/day, 0.6 times the MRHD on a mg/m^2 basis.

17 SUPPORTING PRODUCT MONOGRAPHS

1) FETZIMA® (Levomilnacipran Extended Release Capsules, 20 mg, 40 mg, 80 mg and 120 mg), submission control 272055, Product Monograph, AbbVie Corporation. (AUG 11, 2023)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]APO-LEVOMILNACIPRAN

Levomilnacipran Extended Release Capsules

Read this carefully before you start taking **APO-LEVOMILNACIPRAN** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APO-LEVOMILNACIPRAN**.

Serious Warnings and Precautions

New or worsened emotional or behaviour problems:

- When you first start taking APO-LEVOMILNACIPRAN 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 APO-LEVOMILNACIPRAN, 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 APO-LEVOMILNACIPRAN.
- 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 your medicine as it takes time for APO-LEVOMILNACIPRAN to work.

Self-harm or Suicide

- Antidepressants, such as APO-LEVOMILNACIPRAN, can increase the risk of suicidal thoughts or actions.
- If you have thoughts of harming or killing yourself at any time, tell your healthcare professional or go to a hospital right away. You will be closely observed by your healthcare professional in this situation.

What is APO-LEVOMILNACIPRAN used for?

APO-LEVOMILNACIPRAN is used in adults to relieve the symptoms of:

- Depression (feeling sad, change in appetite or weight, difficulty concentrating or sleeping, loss of interest in usual activities, unexplained aches and pains, feeling tired, headaches or suicidal thoughts)

How does APO-LEVOMILNACIPRAN work?

APO-LEVOMILNACIPRAN belongs to a class of medicines called serotonin and norepinephrine reuptake inhibitors (SNRI). It is thought to work by affecting two naturally occurring brain chemicals, serotonin and norepinephrine.

What are the ingredients in APO-LEVOMILNACIPRAN?

Medicinal ingredients: Levomilnacipran (as levomilnacipran hydrochloride)

Non-medicinal ingredients: Ammonium hydroxide, ethyl cellulose, hypromellose, iron oxide black, iron oxide red, iron oxide yellow, potassium hydroxide, povidone, propylene glycol, shellac, sugar spheres, talc, titanium dioxide and triethyl citrate.

APO-LEVOMILNACIPRAN comes in the following dosage forms:

Capsules: 20 mg, 40 mg, 80 mg and 120 mg.

Do not use APO-LEVOMILNACIPRAN if you:

- are allergic to levomilnacipran, milnacipran or any of the other ingredients in APO-LEVOMILNACIPRAN (see **What are the ingredients in APO-LEVOMILNACIPRAN?**)

- take a Monoamine Oxidase Inhibitor (MAOI). Ask your healthcare professional if you are not sure you are taking a MAOI, including the antibiotic linezolid and methylene blue.

  - do not take a MAOI within 2 weeks of stopping APO-LEVOMILNACIPRAN unless directed to do so by your healthcare professional

  - do not start APO-LEVOMILNACIPRAN if you stopped taking a MAOI in the last 2 weeks unless directed to do so by your healthcare professional

- have had the following conditions:

  - recent heart attack or severe heart failure

  - racing heart rate or high blood pressure that cannot be controlled

  - history of stroke

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

- are taking any other medicines

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

- have a history of high blood pressure or abnormally fast heartbeat

- have a history of medical conditions including heart problems, seizures or kidney problems

- have a history of drug abuse. Your healthcare professional may monitor you for signs of misuse or abuse while you take APO-LEVOMILNACIPRAN.

- have diabetes and are taking insulin or other medicines to lower your blood sugar. APO-LEVOMILNACIPRAN may affect your blood sugar levels. Closely monitor your blood sugar levels while taking it.

- have a history of urinary disorders

- have a bleeding disorder or have been told that you have low platelets in your blood

- have a history of low sodium levels in your blood

- have a condition that causes abnormally high pressure in your eye, such as glaucoma

- have a family history of mania or bipolar disorder

- have a history of sexual problems

Other warnings you should know about:

Do not stop taking APO-LEVOMILNACIPRAN without first talking to your healthcare professional. Stopping APO-LEVOMILNACIPRAN suddenly may cause symptoms, including:

- anxiety, irritability, high or low mood, feeling restless or sleepy

- headache, sweating, nausea, dizziness

- electric shock-like sensations, tremor, confusion

Your healthcare professional will safely and gradually taper your dose if it is decided that you should stop taking APO-LEVOMILNACIPRAN.

APO-LEVOMILNACIPRAN can cause serious side effects, including:

- **Serotonin toxicity (also known as serotonin syndrome):** APO-LEVOMILNACIPRAN can cause serotonin toxicity, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You

may develop serotonin toxicity if you take APO-LEVOMILNACIPRAN with certain anti-depressants or migraine medications.

Serotonin toxicity symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

- **Hypertension** (high blood pressure): If you have high blood pressure, it should be controlled before your start taking APO-LEVOMILNACIPRAN.

- **Tachycardia** (abnormally fast heartbeat): If you have heart problems, including an abnormally fast heartbeat, your problems should be treated before you start taking APO-LEVOMILNACIPRAN.

- **Problems with urination**: APO-LEVOMILNACIPRAN may cause you to have problems with urination including decreased urine flow and being unable to pass any urine. This mostly affects males.

- **Hyponatremia** (low sodium in the blood): APO-LEVOMILNACIPRAN may cause low sodium levels in your blood. This condition may be serious and even cause death. Elderly people may be at greater risk for this.

- **Seizures** (fit)

- **Angle-Closure Glaucoma** APO-LEVOMILNACIPRAN can cause an acute attack of glaucoma. Having your eyes examined before you take APO-LEVOMILNACIPRAN 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.

- **Mania/hypomania**: APO-LEVOMILNACIPRAN may cause manic episodes, especially if you have a history of mania or bipolar disorder.

See the **Serious side effects and what to do about them** table below for more information on these and other serious side effects.

Increased risk of bleeding: Taking APO-LEVOMILNACIPRAN with acetylsalicylic acid (ASA, or Aspirin), non-steroidal anti-inflammatory drugs (NSAIDs) (e.g. ibuprofen, celecoxib, naproxen), warfarin or other blood thinners may increase your risk of bleeding. This includes:

- Gastrointestinal (GI) bleeding, which can happen anywhere along the GI tract between the mouth and anus. Symptoms of GI bleeding include: blood in vomit, black tarry stools, bright red blood in your stool or coming from the anus
- Bleeding under the skin, or bruising
- Nosebleeds
- Hemorrhages (blood loss inside or outside the body), which can be life-threatening

Tell your healthcare professional **right away** if you have any unusual bleeding or bruising.

Increased risk of breaking a bone: Taking APO-LEVOMILNACIPRAN may increase your risk of breaking a bone if you are elderly, have osteoporosis or have other major risk factors for breaking a bone. You should take extra care to avoid falls, especially if you get dizzy or have low blood pressure.

Driving and using machines: Before doing any tasks that require special attention, wait until you know how you respond to APO-LEVOMILNACIPRAN.

Children and adolescents: APO-LEVOMILNACIPRAN is not to be used in children and adolescents under 18 years of age.

Pregnancy:

- Tell your healthcare professional **right away** if you become pregnant while taking APO-LEVOMILNACIPRAN. It is very important that you do **not** stop taking APO-LEVOMILNACIPRAN without first consulting with your healthcare professional.
- If you are pregnant, your healthcare professional will decide if APO-LEVOMILNACIPRAN is right for you. They will also discuss with you the risk of complications after birth if you take it during pregnancy.
- If you take APO-LEVOMILNACIPRAN near the end of your pregnancy, you may be at higher risk of heavy vaginal bleeding shortly after birth.
- If you have been prescribed APO-LEVOMILNACIPRAN during pregnancy, be ready to seek immediate medical help for your newborn if they:

- Have trouble breathing or feeding
- Have muscle stiffness, or floppy muscles (like a rag doll)
- Have seizures (fits)
- Are shaking (jitteriness)
- Are constantly crying

Breastfeeding: It is not known if levomilnacipran can pass into your breastmilk and harm your baby. Talk to your healthcare professional about ways to feed your baby while taking APO-LEVOMILNACIPRAN.

Check-ups and testing: Your healthcare professional may do tests, including blood tests, before you take APO-LEVOMILNACIPRAN and regularly during your treatment. These tests will monitor:

- your blood pressure
- your heart rate
- your level of cholesterol (a type of fat) in your blood
- your blood sugar levels

Your healthcare professional will also closely monitor you while you are taking APO-LEVOMILNACIPRAN for any changes in your behaviour or emotions or thoughts of suicide.

Depending on your test results, your healthcare professional may adjust your dose or discontinue your treatment with APO-LEVOMILNACIPRAN.

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

Serious Drug Interactions

Do not take APO-LEVOMILNACIPRAN if you:

- are taking or have recently taken (in the last 14 days) any monoamine oxidase inhibitors (MAOIs) such as phenelzine, tranylcypromine, moclobemide, linezolid, methylene blue, isocarboxazid, isoniazid as you may have serious side effects

Taking APO-LEVOMILNACIPRAN with any of these medicines may cause serious drug interactions. Ask your healthcare professional if you are unsure.

The following may interact with APO-LEVOMILNACIPRAN:

- other antidepressants
- other medicines that affect serotonin such as lithium, linezolid, sibutramine, tryptophan, triptans, St. John's Wort
- certain medicines that may affect blood clotting and increase bleeding, such as oral blood thinners (e.g., warfarin, dabigatran), acetylsalicylic acid (ASA, or Aspirin) and other NSAIDs (e.g., ibuprofen, celecoxib, naproxen)
- certain medicines used to treat pain, such as fentanyl (used in anaesthesia or to treat chronic pain), tramadol, tapentadol, meperidine, methadone, pentazocine
- certain medicines used to treat cough, such as dextromethorphan
- ketoconazole, a medicine used to treat fungal infections
- medicines used to treat high blood pressure such as clonidine, methyldopa, diuretics (also known as "water pills")

As with other drugs that affect the brain, use of alcohol is not recommended when taking APO-LEVOMILNACIPRAN.

How to take APO-LEVOMILNACIPRAN:

- APO-LEVOMILNACIPRAN should be taken once a day, with or without food. The capsules should be swallowed whole. Do not open, chew or crush the capsule.

Usual dose:

- Take APO-LEVOMILNACIPRAN exactly as your healthcare professional tells you
- Never change your dose without first consulting your healthcare professional
- Do not stop taking APO-LEVOMILNACIPRAN without first talking to your healthcare professional

Overdose:

If you think you, or a person you are caring for, have taken too much APO-LEVOMILNACIPRAN, contact a 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 or symptoms.

Missed Dose:

If you miss a dose of APO-LEVOMILNACIPRAN by a few hours, take the dose as soon as you remember. If it is almost time for the next dose, skip the missed dose and take the next dose at your usual time. Do not take two doses at one time.

What are possible side effects from using APO-LEVOMILNACIPRAN?

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

Side effects may include:

- Nausea
- Sexual problems
- Excessive sweating
- Constipation
- Gas
- Trouble sleeping
- Vomiting
- Dry mouth
- Abdominal pain
- Sore throat or runny nose
- Hot flashes
- Loss of appetite
- Dry eyes
- Feeling thirsty
- Headache
- Tingling sensation in hands or feet
- Teeth grinding
- Weight loss
- Nosebleeds

APO-LEVOMILNACIPRAN can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations		✓	
Problems with urination: decreased urine flow or inability to pass any urine		✓	
Rash alone		✓	
Tachycardia (abnormally fast heartbeat)		✓	
UNCOMMON			
Hives		✓	
Mania/Hypomania: elevated or irritated mood, decreased need for sleep, racing thoughts		✓	
RARE			
Angle-Closure Glaucoma: Eye pain, changes in vision, and swelling or redness in or around the eye			✓
Seizures (fit): loss of consciousness with uncontrollable shaking			✓
UNKNOWN FREQUENCY			
Allergic reactions: red skin, hives, itching, swelling of the lips, face, tongue or throat, trouble breathing, wheezing, shortness of breath, skin rashes, blisters of the skin, sores or pain in the mouth or eyes.			✓
Hyponatremia (low sodium in the blood): symptoms of tiredness, weakness, confusion, combined with achy, stiff or uncoordinated muscles, seizure, coma		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
New or worsened emotional or behavioural problems: • feeling very agitated or restless • acting aggressive • being angry or violent • feeling anxious • acting on dangerous impulses • thoughts of harming others		✓	
Self-harm and suicide: Have thoughts of harming or killing yourself			✓
Serotonin toxicity: a reaction which may cause feelings or agitation or restlessness, flushing, muscle twitching, involuntary eye movements, heavy sweating, high body temperature (>38 °C), or rigid muscles			✓
Thrombocytopenia (low blood platelets): Bruising or unusual bleeding from the skin or other areas		✓	

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:

Store at room temperature 15°C to 30°C.

Keep out of reach and sight of children.

If you want more information about APO-LEVOMILNACIPRAN:

- Talk to your healthcare professional

- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (http://www.apotex.ca/products), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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