PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr FETZIMA™

levomilnacipran extended-release capsules

20 mg, 40 mg, 80 mg and 120 mg levomilnacipran (as levomilnacipran hydrochloride)

Antidepressant

Actavis Specialty Pharmaceuticals Co.
6733 Mississauga Road, Suite 400
Mississauga, Ontario
L5N 6J5
www.actavis.ca

Date of Preparation:

May 7, 2015

Submission Control No: 167319

Table of Contents

[Pr]FETZIMA™

levomilnacipran extended-release capsules
(as levomilnacipran hydrochloride)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Extended-Release Capsule 20 mg, 40 mg, 80 mg, 120 mg	Ethylcellulose, hypromellose, iron oxide black, iron oxide yellow (20 mg and 40 mg), iron oxide red (80 mg and 120 mg), povidone, shellac glaze, sugar spheres, talc, titanium dioxide, triethyl citrate

INDICATIONS AND CLINICAL USE

Adults
FETZIMA (levomilnacipran extended-release capsules) is indicated for the short-term symptomatic relief of major depressive disorder (MDD).

The efficacy of FETZIMA was established in randomized, double-blind, placebo-controlled trials of up to 8 weeks (see CLINICAL TRIALS). Long-term maintenance of effect has not been established.

Geriatrics (> 65 years of age):
Caution should be exercised in treating the elderly. Clinical studies of FETZIMA 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 WARNINGS AND PRECAUTIONS, Special Populations).

Pediatrics (< 18 years of age): FETZIMA is not indicated for use in patients under the age of 18. Safety and efficacy in the pediatric population have not been established (see WARNINGS AND PRECAUTIONS, Potential Association with Behavioural and Emotional Changes, Including Self-Harm).

CONTRAINDICATIONS

- **Hypersensitivity:** Patients who are hypersensitive to levomilnacipran, milnacipran or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.

- **Serotonin Syndrome and Monoamine Oxidase Inhibitors (MAOIs):** FETZIMA (levomilnacipran extended-release capsules) 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 FETZIMA 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.

- **Cardiovascular:** FETZIMA 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

WARNINGS AND PRECAUTIONS

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 (see OVERDOSAGE).

Discontinuation Symptoms

Patients currently taking FETZIMA (levomilnacipran extended-release capsules) 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 FETZIMA

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, headache, 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 FETZIMA. Reduce the dose gradually whenever possible (see DOSAGE AND ADMINISTRATION, 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 FETZIMA. 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 FETZIMA, 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 FETZIMA.

Elevated Blood Pressure and Hypertension

In short-term, placebo-controlled studies in patients with MDD, FETZIMA (40 mg - 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 FETZIMA-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 ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology & Hemodynamics).

In patients exposed to one-year, open-label treatment of FETZIMA (doses from 40-120 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 FETZIMA – treated patients (see Table 1). Dose-dependency was not evident over the 40-120 mg dose range studied. For patients who experience a sustained increase in blood pressure while receiving FETZIMA, discontinuation or other appropriate medical intervention should be considered.

Table 1: Incidence of Patients with Sustained Hypertension for All Short-Term Clinical Studies

Criteria	**Placebo**	**FETZIMA (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%

Concomitant use of FETZIMA with drugs that increase blood pressure has not been evaluated and such combination should be used with caution (see DRUG INTERACTIONS).

Blood pressure should be measured prior to initiating treatment and periodically throughout FETZIMA treatment (see Monitoring and Laboratory Tests). Pre-existing hypertension and other cardiovascular disease should be treated and stabilized before starting therapy with FETZIMA. Centrally acting antihypertensives (clonidine, methyldopa, etc.) were not permitted in the clinical studies and may interact with FETZIMA (see DRUG INTERACTIONS, Central Nervous System (CNS) Active Agents).

Elevated Heart Rate

SNRIs, including FETZIMA, 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, FETZIMA 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 FETZIMA (doses from 40-120 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, FETZIMA 120 mg/day was associated with a maximum placebo-adjusted increase from baseline in heart rate of 20.2 bpm (see ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology and Hemodynamics).

Concomitant use of FETZIMA with drugs that increase heart rate has not been evaluated and the possibility of additive effects should be considered. FETZIMA 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 FETZIMA treatment (see Monitoring and Laboratory Tests). Pre-existing tachyarrhythmias and other cardiac disease should be treated before starting therapy with FETZIMA. Patients with serious or uncontrolled tachyarrhythmias, ischemic heart disease, or congestive heart failure should not receive FETZIMA (see CONTRAINDICATIONS). For patients who experience an increase in heart rate while receiving FETZIMA discontinuation or other appropriate medical intervention should be considered.

Dependence/Tolerance

Dependence and Abuse

FETZIMA 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 FETZIMA (e.g., development of tolerance or drug-seeking behavior).

Endocrine and Metabolism

Diabetic Patients

FETZIMA 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). FETZIMA should be used with caution in diabetic patients on insulin or other antidiabetic drugs (see Monitoring and Laboratory Tests).

Genitourinary

Urinary Hesitation, Retention and Dysuria

The noradrenergic effect of SNRIs including FETZIMA, 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 FETZIMA 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 FETZIMA, 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 FETZIMA 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 FETZIMA, 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.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of FETZIMA and NSAIDs, ASA, or other drugs that affect coagulation (see DRUG INTERACTIONS, Drugs Affecting Platelet Function). Caution is advised in patients with a history of bleeding disorder or predisposing conditions (e.g. thrombocytopenia).

Neurologic

Seizures

FETZIMA 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 FETZIMA. Like other antidepressants, FETZIMA should be prescribed with caution in patients with a seizure disorder.

Serotonin Syndrome

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

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

The concomitant use of FETZIMA with MAOIs intended to treat psychiatric disorders is contraindicated. FETZIMA 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 FETZIMA. FETZIMA should be discontinued before initiating treatment with the MAOI (see CONTRAINDICATIONS, DRUG INTERACTIONS, and DOSAGE AND ADMINISTRATION).

If concomitant use of FETZIMA with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

The concomitant use of FETZIMA with serotonin precursors (such as tryptophan) is not recommended.

Treatment with FETZIMA and any concomitant serotonergic agent should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Ophthalmologic

Narrow Angle Glaucoma

As with other SSRIs/SNRIs, FETZIMA can cause mydriasis and should be used with caution in patients with raised intraocular pressure or those with narrow-angle glaucoma.

Psychiatric

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 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 FETZIMA-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 FETZIMA 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 FETZIMA 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 DOSAGE AND ADMINISTRATION, Renal Impairment).

Sexual Function/Reproduction

Refer to ADVERSE REACTIONS, Sexual Function.

Special Populations

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 FETZIMA (one premature birth and one preeclampsia) out of 6 confirmed pregnancies with adequate follow-up. The causal relationship between FETZIMA and the emergence of these events has not been established. FETZIMA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 WARNINGS AND PRECAUTIONS, Serotonin Syndrome).

Labour and Delivery
The effect of FETZIMA on labour and delivery in humans is unknown. FETZIMA should be used during labour and delivery only if the potential benefits outweigh the potential risks.

Nursing Women
There are no adequate and well-controlled studies in nursing mothers. It is not known if FETZIMA 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 FETZIMA, 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 FETZIMA should be considered only if the potential benefits outweigh the potential risks to the child.

Pediatrics (<18 years of age)
FETZIMA is not indicated for use in children under 18 years of age (see WARNINGS AND PRECAUTIONS, Potential Association with Behavioral and Emotional Changes, Including Self-Harm).

Geriatrics (> 65 years of age)
Of the total number of FETZIMA-treated subjects in 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 WARNINGS AND PRECAUTIONS, Hyponatremia, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

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 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 FETZIMA and periodically throughout treatment. For patients who experience a sustained increase in blood pressure or heart rate while receiving FETZIMA, 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 heart beat and possibly more rapid, palpitations, dizziness, easy fatigability, blurred vision, chest pain (See also WARNINGS and PRECAUTIONS, Cardiovascular).

Serum Cholesterol

Clinically relevant increases in total serum cholesterol were recorded in 5% of patients receiving 40-120 mg/day of FETZIMA in short-term clinical trials, and in 7% of patients exposed to one-year, open-label treatment (doses from 40-120 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 FETZIMA. Patients should be monitored for signs and symptoms of glucose fluctuations. Diabetic patients especially should have their glycaemia carefully monitored.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety of FETZIMA (levomilnacipran extended-release capsules) was evaluated in 2,673 patients (18-78 years of age) diagnosed with MDD who participated in clinical studies. Among the 2,673 FETZIMA-treated patients, 1,583 were exposed to FETZIMA in short-term, placebo-controlled studies.

A total of 737 patients were exposed to FETZIMA for at least 6 months and 367 were exposed for one year. In these studies FETZIMA was given at doses ranging from 40-120 mg once daily and was given without regard to food.

The most commonly observed adverse events in FETZIMA-treated MDD patients in placebo-controlled studies (incidence ≥ 5% and at least twice the rate of placebo) were: nausea, heart rate increased, erectile dysfunction, hyperhydrosis, 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 FETZIMA (40-120 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 FETZIMA-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, FETZIMA treatment was associated with mean increases in blood pressure and heart rate (see WARNINGS AND PRECAUTIONS, Cardiovascular). The most commonly reported cardiovascular adverse events among FETZIMA-treated patients in the short-term clinical studies included heart rate increased, tachycardia, palpitations, hypertension, hypotension, and blood pressure increased (see Table 2).

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

Table 2 shows the incidence of adverse events that occurred in ≥ 2% of FETZIMA-treated MDD patients (and greater than placebo-treated patients) in the placebo-controlled studies.

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

System Organ Class Preferred Term	Placebo N =1040 (%)	FETZIMA 40-120 mg/d N = 1583 (%)
Gastrointestinal disorders		
Nausea	6	17
Dry mouth	7	10
Constipation	3	9
Vomiting	1	5
Abdominal Pain	3	5
Nervous system disorders		
Headache[a]	14	17
Dizziness	5	8
Skin and subcutaneous tissue disorders		
Hyperhidrosis	2	9
Rash	<1	2
Cardiac disorders		
Tachycardia[a]	2	6
Palpitations	1	5
Reproductive system and breast disorders[b]		
Erectile dysfunction[b]	1	6
Testicular pain[b]	<1	4
Ejaculation disorder[b]	<1	5
Investigations		
Heart rate increased[a]	1	6
Blood pressure increased[a]	1	3
Psychiatric disorders		
Insomnia[a]	4	6
Anxiety	1	2
Infections and infestations		
Upper respiratory tract infection[a]	4	5
Nasopharyngitis	3	4
Renal and urinary disorders		
Urinary hesitation	0	4
Vascular disorders		
Hot flush	1	3
Hypertension[a]	1	3
Hypotension	1	3
Metabolism and nutrition disorders		
Decreased appetite	1	3

[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 FETZIMA across the dose range 40-120 mg/day, with the exception of erectile dysfunction and urinary hesitation (see Table 3).

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

System Organ Class Preferred Term	Placebo N = 362 (%)	FETZIMA		
		40 mg/day N = 366 (%)	80 mg/day N = 367 (%)	120 mg/day N = 180 (%)
Urinary hesitation	0	4	5	6
Erectile dysfunction[a]	2	6	8	10

[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 4 shows the incidence of adverse events associated with sexual dysfunction in FETZIMA-treated patients in placebo controlled short-term studies.

Table 4: Adverse Events Associated With Sexual Dysfunction by Sex in Five, Short-term Phase 3 Placebo-Controlled Studies

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

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

Less Common Clinical Trial Adverse Drug Reactions (<2%)
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: *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 disorders: *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 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, FETZIMA-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 FETZIMA 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.

Abnormal Hematologic and Clinical Chemistry Findings
Slight elevations of liver enzyme levels (ALT, AST, and ALP) were noted among FETZIMA-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 FETZIMA-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 FETZIMA with enzyme levels returning to normal during on-going treatment. No patient had concurrent PCS elevations in ALT or AST and total bilirubin.

DRUG INTERACTIONS

Serious Drug Interactions

Monoamine Oxidase Inhibitors (MAOIs): See CONTRAINDICATIONS and Drug-Drug Interactions- Monoamine Oxidase Inhibitors (MAOIs)

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

Drug-Drug Interactions
Monoamine Oxidase Inhibitors (MAOIs)
FETZIMA is contraindicated in patients taking MAOIs, or within at least 14 days of discontinuation (See CONTRAINDICATIONS, Monoamine Oxidase Inhibitors (MAOIs), WARNINGS AND PRECAUTIONS, Serotonin Syndrome and DOSAGE AND ADMINISTRATION, Switching to or from Monoamine Oxidase Inhibitor (MAOI) Antidepressants).

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 FETZIMA 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 WARNINGS AND PRECAUTIONS, Neurologic, Serotonin Syndrome).

Drug that Increase Heart Rate and/or Blood Pressure
FETZIMA increases heart rate and blood pressure. FETZIMA 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 FETZIMA in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised when FETZIMA 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 FETZIMA is initiated or discontinued (See WARNINGS AND PRECAUTIONS, Hematologic, Abnormal Bleeding).

Potential for Other Drugs to Affect FETZIMA

Inhibitors of CYP3A4: Metabolism plays a limited role in levomilnacipran elimination. CYP3A4 is a major enzyme catalyzing desethylation of levomilnacipran to desethyl levomilnacipran. Concomitant use of FETZIMA and ketoconazole, a potent inhibitor of CYP3A4, can increase levomilnacipran plasma exposure (C_{max} by 39% and AUC by 57%). Concomitant use of FETZIMA with potent inhibitors of CYP3A4 may result in higher concentrations of FETZIMA.

Inducers of CYP3A4: Concomitant use of FETZIMA with carbamazepine, an inducer of CYP3A4, can reduce levomilnacipran plasma exposure (C_{max} by 26% and AUC by 29%). No dosing adjustment is recommended when FETZIMA is co-administered with inducers of CYP3A4.

Substrates of CYP3A4: Concomitant use of FETZIMA with alprazolam, a substrate of CYP3A4, had no significant effect on levomilnacipran plasma exposure. No dosing adjustment is recommended when FETZIMA is co-administered with substrates of CYP3A4.

Inhibitors of Other CYP Enzymes: Concomitant administration of FETZIMA with inhibitors of CYP2C8, CYP2C19, CYP2D6, and CYP2J2 is not expected to significantly alter plasma concentrations of levomilnacipran. *In vitro* studies have shown that these isoenzymes have minimal contributions to metabolism of levomilnacipran.

Potential for FETZIMA to Affect Other Drugs

Drugs Metabolized by CYP3A4: Based on *in vitro* data, levomilnacipran slightly inhibits CYP3A4. However, concomitant use of FETZIMA with alprazolam or carbamazepine, substrates of CYP3A4, had no significant effect on alprazolam or carbamazepine plasma exposure. No dosing adjustment is recommended.

Drugs Metabolized by CYP2C9: Based on *in vitro* data, levomilnacipran slightly inhibits CYP2C9. No dosing adjustment is recommended for substrates of CYP2C9.

Drugs Metabolized by Other CYP Enzymes: Based on *in vitro* data, drugs that are substrates of CYP1A2, CYP2A6, CYP2C8, CYP2C19, CYP2D6, and CYP2E1 are not expected to be affected by the co-administration of FETZIMA.

Potential Interaction with Membrane Transporters: *In vitro* evaluations indicated that levomilnacipran does not significantly interact with P-glycoprotein, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2. These data indicate the potential for interactions of levomilnacipran with these membrane transporters is low.

Drugs Highly Bound to Plasma Protein: Because levomilnacipran has low protein binding (22%), it is unlikely to interact with highly protein bound drugs.

Drug-Food Interactions
Food has no clinically meaningful effect on the bioavailability of levomilnacipran. FETZIMA 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).

Drug-Herb Interactions
Interactions with herbs have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions
Alcohol : As with other psychotropic medications, the use of alcohol by patients taking FETZIMA is not recommended.

Interference with Cognitive and Motor Performance
Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that FETZIMA therapy does not adversely affect their ability to engage in such activities.

DOSAGE AND ADMINISTRATION

Dosing Considerations

FETZIMA (levomilnacipran extended-release capsules) is not indicated for use in children under 18 years of age (see WARNINGS AND PRECAUTIONS, Potential Association with Behavioural and Emotional Changes, Including Self-harm).

FETZIMA should be swallowed whole. Do not open, chew or crush the capsule. FETZIMA can be taken with or without food.

Recommended Dose and Dosage Adjustment

Adults

Initial Treatment of Major Depressive Disorder: The recommended dose range for FETZIMA is 40 mg to 120 mg once daily. FETZIMA 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

Efficacy of FETZIMA was established in randomized, double-blind, placebo-controlled studies of up to 8 weeks. It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. There is insufficient evidence available to assess the efficacy of FETZIMA over sustained periods of therapy.

Physicians choosing to use FETZIMA should periodically reassess patients to determine the need for continued treatment.

Pregnant Women

Serious adverse events were reported in two pregnant women exposed to FETZIMA (one premature birth and one preeclampsia). The causal relationship between FETZIMA and the emergence of these events has not been established. Neonates exposed to SNRIs or SSRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women). When treating pregnant women with FETZIMA, the physician should consider the potential risks and benefits of treatment.

Nursing Mothers

There are no clinical data regarding the effect of FETZIMA on lactation and nursing (see WARNINGS AND PRECAUTIONS, Special Populations, Nursing Women). However, studies have shown that levomilnacipran is excreted into the milk of lactating rats. Breastfeeding in women treated with FETZIMA should be considered only if the potential benefits outweigh the potential risks.

Hepatic Impairment
No dose adjustment is required in patients with mild, moderate or severe hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Renal Impairment
Based on a population pharmacokinetic analysis, no dose adjustment is necessary in patients with mild renal impairment (creatinine clearance of 60-89 mL/min). For patients with moderate renal impairment (creatinine clearance of 30-59 mL/min), the dose should not exceed 80 mg/day. For patients with more severe renal impairment (creatinine clearance of 15-29 mL/min) the dose should not exceed 40 mg/day (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Geriatric Patients (> 65 years of age)
No dose adjustment is required in geriatric patients on the basis of age (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions). In a multiple-dose clinical pharmacokinetic study, elderly subjects (> 65 years) had a slightly higher exposure (Cmax by 24% and AUC by 26%) of levomilnacipran than younger subjects (18-45 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)
FETZIMA is not indicated for use in patients under the age of 18. Safety and efficacy in the pediatric population have not been established. (see WARNINGS AND PRECAUTIONS, Potential Association with Behavioural and Emotional Changes, Including Self-Harm).

Gender
No dose adjustment is required based on gender (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Discontinuing Treatment
Discontinuation symptoms have been reported with discontinuation of serotonergic drugs such as FETZIMA. Gradual dose reduction is recommended, instead of abrupt discontinuation, whenever possible. Monitor patients for these symptoms when discontinuing FETZIMA. 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 WARNINGS AND PRECAUTIONS, Discontinuation Symptoms).

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 FETZIMA. Conversely, at least 14 days should be allowed after stopping FETZIMA before starting an MAOI antidepressant (see CONTRAINDICATIONS and DRUG INTERACTIONS).

Use of FETZIMA with Other Drugs that Inhibit Monoamine Oxidase such as Linezolid or Methylene Blue

Do not start FETZIMA in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered (see CONTRAINDICATIONS).

In some cases, a patient already receiving FETZIMA 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, FETZIMA 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 FETZIMA 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 FETZIMA is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use (see WARNINGS AND PRECAUTIONS, Neurologic, Serotonin Syndrome).

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 FETZIMA at the same time.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

There is limited clinical experience with FETZIMA (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 FETZIMA 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

FETZIMA (levomilnacipran extended-release capsules) 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.

Pharmacodynamics

Nonclinical studies have shown that levomilnacipran binds with high affinity to the norepinephrine (NE) and serotonin (5-HT) transporters (K_i = 71-91 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-HT1-7), α- and β-adrenergic, muscarinic (M1-5), histamine (H1-4), dopamine (D1-5), 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 19-22 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 5, 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 5: 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

Pharmacokinetics

Following an oral administration, the mean apparent total clearance of levomilnacipran is 21-29 L/h and the apparent volume of distribution is 387-473 L. The pharmacokinetics of levomilnacipran (25-300 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 FETZIMA 120 mg, the mean C_{max} value is 341 ng/mL, and the mean steady-state AUC value is 5196 ng·h/mL.

Absorption: Peak concentration of levomilnacipran is reached at a median of 6-8 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 387-473 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 DRUG INTERACTIONS).

Excretion: 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%).

Dosing adjustment is necessary for patients with moderate or severe renal impairment (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Renal Impairment and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency).

Special Populations and Conditions

Pediatrics: Clinical studies with FETZIMA in pediatric patients have not been conducted; therefore the safety and effectiveness of FETZIMA in the pediatric population have not been established. FETZIMA is not approved for use in pediatric patients (see WARNINGS AND PRECAUTIONS, Potential Association with Behavioural and Emotional Changes, Including Self-Harm).

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 (18-45 years).

Gender: 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 - 79 ml/min), moderate (creatinine clearance of 30 - 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 DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Renal Impairment).

STORAGE AND STABILITY

FETZIMA (levomilnacipran extended-release capsules) should be stored at controlled room temperature (15-30°C).

SPECIAL HANDLING INSTRUCTIONS

No special handling is required.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms: FETZIMA (levomilnacipran extended-release capsules) 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: Each capsule has a yellow cap imprinted with “FL” in black ink, and a white body imprinted with “20” in black ink.

40 mg: Each capsule has a yellow cap imprinted with “FL” in black ink, and a yellow body imprinted with “40” in black ink.

80 mg: Each capsule has a pink cap imprinted with “FL” in black ink, and a white body imprinted with “80” in black ink.

120 mg: Each capsule has a pink cap imprinted with “FL” in black ink, and a pink body imprinted with “120” in black ink.

Composition: FETZIMA contains the following inactive ingredients: ethylcellulose; hypromellose; iron oxide, black; iron oxide, red (80 mg and 120 mg only); iron oxide, yellow (20 mg and 40 mg only); povidone; shellac glaze; sugar spheres; talc; titanium dioxide; triethyl citrate.

Packaging: FETZIMA will be supplied in the following configurations:

Bottles of 30 capsules: 20 mg, 40 mg, 80 mg and 120 mg

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

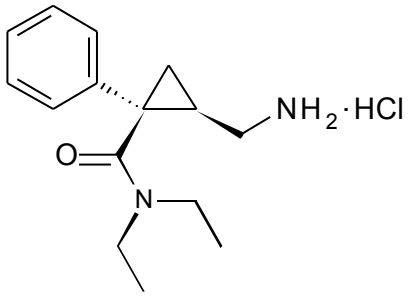
Proper name: Levomilnacipran hydrochloride

Chemical name: (1S,2R)-2-(aminomethyl)-N,N-diethyl-1-phenylcyclopropanecarboxamide hydrochloride

Molecular formula: $C_{15}H_{22}N_2O \cdot HCl$

Molecular weight: 282.8 g/mol

Structural formula:



Physicochemical properties: Levomilnacipran hydrochloride is a white to off-white powder that is very soluble in water and 0.1M HCl and freely soluble in ethanol.

CLINICAL TRIALS

The efficacy of FETZIMA (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 - 120 mg once daily) in adult (18-78 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 FETZIMA-treated subjects in 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 6.

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.

Table 6: Clinical Studies Supporting Efficacy of FETZIMA 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 flexible dose study	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 Results

In three of the four studies (LVM-MD-01, LVM-MD-10, and LVM-MD-03), FETZIMA 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 7).

Table 7: Summary of the Least Square Mean Difference from Placebo in Change from Baseline for MADRS Score, in Placebo-Controlled Studies (ITT Population)

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

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 FETZIMA 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).

FETZIMA 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.

DETAILED PHARMACOLOGY

Pharmacodynamic Studies

Nonclinical studies indicate that levomilnacipran:

- Inhibits the reuptake of serotonin (5-HT) and norepinephrine (NE) *in vitro* with approximately 2-fold greater potency for NE reuptake inhibition than 5-HT (IC_{50} = 11 and 16-19 nM, for NE and 5-HT respectively at human transporters); levomilnacipran does not inhibit dopamine (DA) reuptake.
- Has no significant activity (IC_{50} > 10μM; ~8-fold the exposure of the 120 mg clinical dose) at 80 neuronal targets (i.e. receptors, transporters, or ion channels) other than the NE and 5-HT transporters.
- Increases extracellular levels of NE more potently than 5-HT in the rat frontal cortex and exhibits efficacy in rodent models of depression at comparable doses.

The *in vitro* and *in vivo* pharmacodynamic properties of levomilnacipran are consistent with the properties of antidepressants.

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 μM) produced a concentration-dependent inhibition of the maximum tail current amplitude, with an estimated IC50 > 10 μM.

- The effect of levomilnacipran (0.01, 0.1, 1, and 10 μM) 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 μM and in both APD70 (+22 msec; $p < 0.01$) and ADP90 (+37 msec; $p < 0.01$) at 10 μM 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 - 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.

TOXICOLOGY

Toxicology Program

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.

Carcinogenesis
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.

Mutagenesis
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.

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.

REFERENCES

1. Asnis GM, Bose A, Gommoll CP, Chen C, Greenberg WM. Efficacy and safety of levomilnacipran sustained release 40 mg, 80 mg, or 120 mg in major depressive disorder: A phase 3 randomized, double-blind, placebo-controlled study. J Clin Psychiatry 2013;74(3):242-248.

2. Auclair AL, Martel JC, Assié MB, Bardin L, Heusler P et al. Levomilnacipran (F2695) a norepinephrine-preferring SNRI : Profile in vitro and in models of depression and anxiety. Neuropharmacology 2013;70:338-347.

3. Bakish D, Bose A, Gommoll C, Chen C, Nunez et al. Levomilnacipran ER 40 mg and 80 mg in patients with major depressive disorder: a phase III, randomized, double-blind, fixed-dose, placebo-controlled study. J Psychiatry Neurosci 2014;39(1):40-9.

4. Chen L, Boinpally R, Greenberg WM, Wangsa J, Periclou A, Ghahramani P. Effect of hepatic impairment on the pharmacokinetics of levomilnacipran following a single oral dose of a levomilnacipran extended-release capsule in human participants. Clin Drug Investig 2014;34:351-9.

5. Gommoll CP, Greenberg WM, Chen C. A randomized, double-blind, placebo-controlled study of flexible doses of levomilnacipran ER (40 - 120 mg/day) in patients with major depressive disorder. Journal of Drug Assessment 2014;3:10-19.

6. Mago R, Forero G, Greenberg WM, Gommoll C, Chen C. Safety and tolerability of levomilnacipran ER in major depressive disorder: Results from an open-label, 48-week extension study. Clin Drug Investig 2013; DOI 10.1007/s40261-013-0126-5.

7. Montgomery SA, Gommoll CP, Chen C, Greenberg WM. Efficacy of levomilnacipran extended-release in major depressive disorder: pooled analysis of 5 double-blind, placebo-controlled trials. CNS Spectrums. 2014;June:1-9 Available on CJO 2014 doi:10.1017/S1092852914000273.

8. Montgomery SA, Mansuy L, Ruth A, Bose A, Li H, Li D. Efficacy and safety of levomilnacipran sustained release in moderate to severe major depressive disorder: A randomized, double-blind, placebo-controlled, proof-of-concept study. J Clin Psychiatry 2013; 74(4):363-369.

9. Montgomery SA, Mansuy L, Ruth AC, Li D, Gommoll C. The efficacy of extended-release levomilnacipran in moderate to severe major depressive disorder: secondary and post-hoc analyses from a randomized, double-blind, placebo-controlled study. Int Clin Psychopharmacol 2014;29:26-35.

10. Sambunaris A, Bose A, Gommoll CP, Chen C, Greenberg WM, Sheehan DV. A phase III, double-blind, placebo-controlled, flexible-dose study in levomilnacipran extended-release in patients with major depressive disorder. J Clin Psychopharmacol 2013;34(1).

11. Sambunaris A, Gommoll C, Chen C, Greenberg WM. Efficacy of levomilnacipran extended-release in improving functional impairment associated with major depressive disorder: pooled analyses of five double-blind, placebo-controlled trials. Int Clin Psychopharmacol 2014;00:00-00.

11. Shiovitz T, Greenberg WM, Chen C, Forero G, Gommoll CP. A randomized, double-blind, placebo-controlled trial of the efficacy and safety of levomilnacipran ER 40 - 120 mg/day for prevention of relapse in patients with major depressive disorder. Innov Clin Neurosci 2014;11(1-2):10-22.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

[Pr]FETZIMA™
levomilnacipran extended-release capsules
(as levomilnacipran hydrochloride)

Read this carefully before you start taking **FETZIMA** 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 **FETZIMA**.

What is FETZIMA used for?
FETZIMA has been prescribed by your doctor to relieve your symptoms of depression which may include feeling sad, loss of interest in usual activities, significant change in weight or appetite, change in sleeping habits, difficulty concentrating, feeling tired or suicidal thoughts. Treatment with these types of medications is most safe and effective when you and your doctor have good communication about how you are feeling.

How does FETZIMA work?
FETZIMA 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 FETZIMA?
Medicinal ingredients: Levomilnacipran (as levomilnacipran hydrochloride)

Non-medicinal ingredients: ethylcellulose, hypromellose, iron oxide - black, iron oxide - red (80 mg and 120 mg only), iron oxide - yellow (20 mg and 40 mg only), povidone, shellac glaze, sugar spheres, talc, titanium dioxide and triethyl citrate.

FETZIMA comes in the following dosage forms:
Capsules of 20 mg, 40 mg, 80 mg and 120 mg.

Do not use FETZIMA if you:

- are allergic to levomilnacipran or any of the other ingredients in FETZIMA (see **What are the ingredients in Fetzima?**)

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

    - Do not take an MAOI within 2 weeks of stopping FETZIMA unless directed to do so by your physician

    - Do not start FETZIMA if you stopped taking an MAOI in the last 2 weeks unless

directed to do so by your physician

- 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

Warnings and Precautions
FETZIMA is not for use in children under 18 years of age.

New or Worsened Emotional or Behavioural Problems
Particularly in the first few weeks or when doses are adjusted, a small number of patients taking drugs of this type may feel worse instead of better. They may experience new or worsened feelings of agitation, hostility, anxiety, impulsivity, or thoughts about suicide, self-harm or harm to others. Suicidal thoughts and actions can occur in any age group but may be more likely in patients 18 to 24 years old. Should this happen to you, or those in your care, **consult your doctor immediately.** Close observation by a doctor is necessary in this situation. **Do not discontinue your medication on your own.**

You may be more likely to think like this if you have previously had thoughts about harming yourself.

You may find it helpful to tell a relative or close friend that you are depressed and ask them to read this leaflet. You might ask them to tell you if they think your depression is getting worse, or if they are worried about changes in your behaviour.

Taking FETZIMA may increase your risk of breaking a bone if you are elderly or 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.

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

- have had a recent bone fracture or were told you have osteoporosis or risk factors for osteoporosis
- have a history of high blood pressure
- have a history of medical conditions including heart problems, seizures or kidney problems
- have a history of urinary disorders

- have a bleeding disorder or have been told that you have low platelets
- have a history of low sodium levels in your blood
- have a family history of mania or bipolar disorder
- are pregnant or thinking about becoming pregnant, or if you are breast feeding or plan to breast feed

Do not stop taking FETZIMA without first talking to your healthcare provider. Stopping FETZIMA suddenly may cause serious symptoms including:

- anxiety, irritability, high or low mood, feeling restless or sleepy
- headache, sweating, nausea, dizziness
- electric shock-like sensations, tremor, confusion

Other warnings you should know about:
If you experience symptoms of severe high blood pressure such as headache (particularly in the back of the head/neck when waking up), a stronger, and possibly more rapid, heartbeat, palpitations, dizziness, fatigue, blurred vision or chest pain, contact your doctor immediately

Do not drive, operating hazardous machinery or do other dangerous activities until you know how FETZIMA affects you.

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

Serious Drug Interactions
When you are taking FETZIMA, you should not take MAOIs (Monoamine Oxidase Inhibitors), or within at least 14 days of discontinuation of the MAOIs. Concomitant use of FETZIMA and MAOI can lead to a serious, sometimes fatal drug interaction called Serotonin Syndrome. Some examples of MAOI include linezolid or intravenous methylene blue, isocarboxazid, isoniazid, tranycypromine and moclobemide etc.

The following may interact with FETZIMA:

- other antidepressants
- other drugs 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 anticoagulants (e.g, warfarin, dabigatran), acetylsalicylic acid (e.g., Aspirin) and other non-steroidal anti-inflammatory drugs (e.g. ibuprofen)

- 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

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

How to take FETZIMA:
FETZIMA 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:
It is very important that you take FETZIMA exactly as your doctor has instructed. Never increase or decrease the dose without consulting your doctor.

Do not stop taking FETZIMA without talking to your doctor.

Overdose:

If you think you have taken too much **FETZIMA**, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose of FETZIMA 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 FETZIMA?

These are not all the possible side effects that you may feel when taking **FETZIMA**. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

Some side effects of FETZIMA include: nausea, rapid or irregular heartbeat, erectile dysfunction, sweating, insomnia, constipation and vomiting.

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 Increased blood pressure		✓	

Fast heartbeat		✓	
Urinary hesitation or inability to urinate		✓	
Rash alone		✓	
UNCOMMON Hives		✓	
Mania/Hypomania: elevated or irritated mood, decreased need for sleep, racing thoughts		✓	
RARE Glaucoma: eye pain, blurred vision and swelling or redness in or around the eye		✓	
Seizures			✓
UNKNOWN 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.			✓
Low platelets: Bruising or unusual bleeding from the skin or other areas		✓	
Serotonin syndrome: a combination or most of the following: confusion, restlessness, sweating, shaking, shivering, high fever, sudden jerking of the muscles, hallucinations, fast heartbeat.			✓
Low sodium level in blood: symptoms of tiredness, weakness, confusion, combined with achy, stiff or uncoordinated muscles.		✓	
SEE WARNINGS AND PRECAUTIONS New or worsened emotional or behavioural problems		✓	

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

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

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

Storage:
Store at 15° to 30°C. Keep out of reach and sight of children.

If you want more information about FETZIMA:

- 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; the manufacturer's website www.actavis.ca, or by calling Actavis Specialty Pharmaceuticals Co. at 1-855-892-8766.

This leaflet was prepared by Actavis Specialty Pharmaceuticals Co.

Last Revised: May 7, 2015