HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FETZIMA safely and effectively. See full prescribing information for FETZIMA.

FETZIMA® (levomilnacipran) extended-release capsules, for oral use
Initial U.S. Approval: 2009 (milnacipran)

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.
- **Increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants (*5.1*).**
- **Monitor for worsening and emergence of suicidal thoughts and behaviors (*5.1*).**
- **FETZIMA is not approved for use in pediatric patients (*8.4*).**

----------INDICATIONS AND USAGE----------
FETZIMA is a serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for the treatment of Major Depressive Disorder (MDD) (*1*).

Limitation of Use: FETZIMA is not approved for the management of fibromyalgia. The efficacy and safety of FETZIMA for the management of fibromyalgia have not been established (*1*).

----------DOSAGE AND ADMINISTRATION----------
- *Recommended dose:* 40 mg to 120 mg once daily with or without food (*2.1*).
- Initiate dose at 20 mg once daily for 2 days and then increase to 40 mg once daily (*2.1*).
- Based on efficacy and tolerability, increase dose in increments of 40 mg at intervals of 2 or more days (*2.1*).
- The maximum recommended dose is 120 mg once daily (*2.1*).
- Take capsules whole; do not open, chew or crush (*2.1*)
- *Renal Impairment:* Do not exceed 80 mg once daily for moderate impairment. Do not exceed 40 mg once daily for severe renal impairment (*2.3*).
- *Discontinuation:* Reduce dose gradually whenever possible (*2.4*)

----------DOSAGE FORMS AND STRENGTHS----------
- Extended-release capsules: 20 mg, 40 mg, 80 mg and 120 mg (*3*).

----------CONTRAINDICATIONS----------
- *Hypersensitivity* to levomilnacipran, milnacipran HCl, or any excipient in the FETZIMA formulation (*4*).
- *Serotonin Syndrome and MAOIs*: Do not use MAOIs intended to treat psychiatric disorders with FETZIMA or within 7 days of stopping treatment with FETZIMA. Do not use FETZIMA within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start FETZIMA in a patient who is being treated with linezolid or intravenous methylene blue (*4*).

----------WARNINGS AND PRECAUTIONS----------
- *Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults*: Monitor patients for clinical worsening and suicidal thinking or behavior (*5.1*).
- *Serotonin Syndrome*: Serotonin syndrome has been reported with SSRIs and SNRIs, both when taken alone, but especially when co-administered with other serotonergic agents (including triptans, tricyclics, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's Wort). If such symptoms occur, discontinue FETZIMA and initiate supportive treatment. If concomitant use of FETZIMA with other serotonergic drugs is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases (*5.2*).
- *Elevated Blood Pressure and Heart Rate*: Measure heart rate and blood pressure prior to initiating treatment and periodically throughout treatment. Control pre-existing hypertension before initiating therapy with FETZIMA (*5.3*, *5.4*).
- *Abnormal Bleeding*: Treatment can increase the risk of bleeding. Caution patients about the risk of bleeding associated with the use of NSAIDs, aspirin, or other drugs that affect coagulation (*5.5*).
- *Angle Closure Glaucoma*: Angle closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants (*5.6*).
- *Urinary Hesitation or Retention*: Can occur. If such symptoms occur, discontinue FETZIMA or consider other appropriate medical intervention (*5.7*).
- *Activation of Mania/Hypomania*: Screen patients for bipolar disorder, Caution patients about risk of activation of mania/hypomania (*5.8*).
- Seizures: Can occur. Use with caution in patients with a seizure disorder (*5.9*).
- *Discontinuation Syndrome*: Taper dose when possible and monitor for discontinuation symptoms (*5.10*).
- *Hyponatremia*: Can occur in association with SIADH (*5.11*).

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo) are: nausea, constipation, hyperhidrosis, heart rate increase, erectile dysfunction, tachycardia, vomiting, and palpitations (*6.1*).

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-678-1605 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- *Strong CYP3A4 inhibitors such as ketoconazole*: Do not exceed 80 mg once daily (*7*).

----------USE IN SPECIFIC POPULATIONS----------
- *Pregnancy*: Based on animal data, may cause fetal harm (*8.1*).

See *17* for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 12/2017

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FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older *[see Warnings and Precautions (5.1)]*.

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber *[see Warnings and Precautions (5.1)]*.

FETZIMA is not approved for use in pediatric patients *[see Use in Specific Populations (8.4)]*.

1 INDICATIONS AND USAGE

FETZIMA, a serotonin and norepinephrine reuptake inhibitor (SNRI) is indicated for the treatment of major depressive disorder (MDD). The efficacy of FETZIMA was established in three 8-week, randomized, double-blind, placebo-controlled studies in adult patients with a diagnosis of MDD *[see Clinical Studies (14)]*.

Limitation of Use: FETZIMA is not approved for the management of fibromyalgia. The efficacy and safety of FETZIMA for the management of fibromyalgia have not been established.

2 DOSAGE AND ADMINISTRATION

2.1 General Instruction for Use

The recommended dose range for FETZIMA is 40 mg to 120 mg once daily, with or without food. FETZIMA should be initiated at 20 mg once daily for 2 days and then increased to 40 mg once daily. Based on efficacy and tolerability, FETZIMA may then be increased in increments of 40 mg at intervals of 2 or more days. The maximum recommended dose is 120 mg once daily.

FETZIMA should be taken at approximately the same time each day. FETZIMA should be swallowed whole. Do not open, chew or crush the capsule.

2.2 Maintenance/Continuation/Extended Treatment

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Patients should be reassessed periodically to determine the need for maintenance treatment and the appropriate dose for treatment. The efficacy of FETZIMA has not been established beyond 8 weeks.

2.3 Special Populations

Renal Impairment: Dose adjustment is not recommended 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 maintenance dose should not exceed 80 mg once daily. For patients with severe renal impairment (creatinine clearance of 15-29 mL/min), the maintenance dose should not exceed 40 mg once daily. FETZIMA is not recommended for patients with end stage renal disease *[see Use in Specific Populations (8.7)]*.

2.4 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 (5.10)]*.

2.5 Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders

At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with FETZIMA. Conversely, at least 7 days should be allowed after stopping FETZIMA before starting an MAOI antidepressant *[see Contraindications (4)]*.

2.6 Use of FETZIMA with Other MAOIs 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 (4)]*.

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 2 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 *[see Warnings and Precautions (5.2)]*.

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 (5.2)]*.

2.7 Use of FETZIMA with Strong Inhibitors of Cytochrome P450 (CYP3A4) Enzyme

The dose of FETZIMA should not exceed 80 mg once daily when used with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, ritonavir) *[see Drug Interactions (7.4)]*

3 DOSAGE FORMS AND STRENGTHS

FETZIMA (levomilnacipran) is available as 20 mg, 40 mg, 80 mg and 120 mg extended-release capsules.

Capsule Strength	Capsule Color/Shape	Capsule Markings
20 mg	yellow cap white body	black "FL" on cap black "20" on body
40 mg	yellow cap yellow body	black "FL" on cap black "40" on body
80 mg	pink cap white body	black "FL" on cap black "80" on body
120 mg	pink cap pink body	black "FL" on cap black "120" on body

4 CONTRAINDICATIONS

- Hypersensitivity to levomilnacipran, milnacipran HCl or to any excipient in the formulation.
- The use of MAOIs intended to treat psychiatric disorders with FETZIMA or within 7 days of stopping treatment with FETZIMA is contraindicated because of an increased risk of serotonin syndrome. The use of FETZIMA within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated *[see Dosage and Administration (2.5) and Warnings and Precautions (5.2)]*.

  Starting FETZIMA in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome *[see Dosage and Administration (2.6) and Warnings and Precautions (5.2)]*.

5 WARNINGS AND PRECAUTIONS

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

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a longstanding concern, however, that

antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phase of treatment. Pooled analyses of short-term placebo-controlled studies of antidepressant drugs (selective serotonin reuptake inhibitors [SSRIs] and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled studies in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term studies of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo controlled studies in adults with MDD or other psychiatric disorders included a total of 295 short-term studies (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric studies. There were suicides in the adult studies, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms: anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major

depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms *[see Dosage and Administration (2.4) and Warnings and Precautions (5.10) for a description of the risks of discontinuation of FETZIMA]*.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers.

Prescriptions for FETZIMA should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

Screening patients for bipolar disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled studies) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that FETZIMA is not approved for use in treating bipolar depression.

5.2 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, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders 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 Dosage and Administration (2.5, 2.6) and Contraindications (4)]*.

If concomitant use of FETZIMA with other serotonergic drugs, including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, amphetamines, and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

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

5.3 Elevated Blood Pressure

SNRIs, including FETZIMA, have been associated with increases in blood pressure. Blood pressure should be measured prior to initiating treatment and periodically throughout FETZIMA treatment. Pre-existing hypertension should be controlled before initiating treatment with FETZIMA. Caution should be exercised in treating patients with pre-existing hypertension, cardiovascular, or cerebrovascular conditions that might be compromised by increases in blood pressure. For patients who experience a sustained increase in blood pressure while receiving FETZIMA, discontinuation or other appropriate medical intervention should be considered.

Table 2 shows the mean changes in blood pressure, sustained hypertension, and upward shifts in hypertensive status that were observed in FETZIMA-treated patients in the short-term placebo-controlled studies.

Table 2 Blood Pressure Mean Changes, Sustained Hypertension, and Upward Shifts in Hypertensive Status

	Placebo	***FETZIMA 40-120 mg/day***
Mean change from baseline to end of treatment, mm Hg		
Systolic blood pressure (SBP)	-0.4	3.0
Diastolic blood pressure (DBP)	-0.0	3.2
Sustained Hypertension, % of patients		
Broad Criteria: SBP ≥ 140 mm Hg and an increase ≥15 mm Hg **OR** DBP ≥ 90 mm Hg and an increase ≥ 10 mm Hg for at least 3 consecutive visits	1.2	1.8
Strict Criteria: SBP ≥ 140 mm Hg and an increase ≥15 mm Hg **AND** DBP ≥ 90 mm Hg and an increase ≥ 10 mm Hg for at least 3 consecutive visits	0.1	0.3
Upward Shifts in Hypertensive Status[a], % of patients		
Normal/ Pre-hypertensive → Stage I/ Stage II	7.1	10.4

[a] Normal Blood Pressure: SBP < 120 mm Hg ***and*** DBP < 80 mm Hg
Pre-hypertension: SBP ≥ 120 mm Hg ***and*** ≤ 139 mm Hg or DBP ≥ 80 mm Hg ***and*** ≤ 89 mm Hg
Stage I hypertension: SBP ≥ 140 mm Hg ***and*** ≤ 159 mm Hg or DBP ≥ 90 mm Hg ***and*** ≤ 99 mm Hg
Stage II hypertension: SBP ≥ 160 mm Hg ***or*** DBP ≥ 100 mm Hg

In the short-term, placebo-controlled MDD studies, the mean increase from initiation of treatment in systolic BP was 3 mm Hg and diastolic BP was 3.2 mm Hg, as compared to no change in the placebo group. There were no dose-related changes in systolic and diastolic blood pressure observed.

In patients exposed to one-year, open-label treatment of FETZIMA (doses range from 40-120 mg once daily), the mean change from initiation of treatment in systolic BP was 3.9 mm Hg and diastolic BP was 3.1 mm Hg.

In the short-term, placebo-controlled studies, 11.6 % of patients met orthostatic hypotension criteria (SBP or DBP) in the FETZIMA group compared to 9.7% in the placebo group. Orthostatic reductions of blood pressure ≥ 10 mm Hg in DBP occurred in 5.8%, 6.1% and 9.8% of FETZIMA-treated patients with doses of 40, 80 and 120 mg/day respectively, compared to 6.2% of placebo-treated patients.

Concomitant use of FETZIMA with drugs that increase blood pressure and heart rate has not been evaluated and such combinations should be used with caution. Effects of FETZIMA on blood pressure in patients with significant hypertension or cardiac disease have not been systematically evaluated. FETZIMA should be used with caution in these patients.

5.4 Elevated Heart Rate

SNRIs including FETZIMA have been associated with increased heart rate. Heart rate should be measured prior to initiating treatment and periodically throughout FETZIMA treatment. Pre-existing tachyarrhythmias and other cardiac disease should be treated before starting therapy with FETZIMA. For patients who experience a sustained increase in heart rate while receiving FETZIMA, discontinuation or other appropriate medical intervention should be considered.

In short-term clinical studies, FETZIMA treatment was associated with a mean increase in heart rate of 7.4 beats per minute (bpm) compared to a mean decrease of 0.3 bpm in placebo-treated patients. Heart rate increase in FETZIMA-treated patients receiving doses of 40 mg, 80 mg and 120 mg was 7.2, 7.2, and 9.1 bpm.

FETZIMA has not been systematically evaluated in patients with a cardiac rhythm disorder.

5.5 Abnormal Bleeding

SSRIs and SNRIs, including FETZIMA, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDS), warfarin, and other anticoagulants may add to this 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 ecchymosis, hematoma, 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, aspirin, or other drugs that affect coagulation or bleeding.

5.6 Angle Closure Glaucoma

The pupillary dilation that occurs following use of many antidepressant drugs including FETZIMA may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

5.7 Urinary Hesitation or Retention

The noradrenergic effect of SNRIs including FETZIMA, can affect urethral resistance. In the controlled short-term studies, urinary hesitation occurred in 4%, 5% and 6% of FETZIMA-treated patients receiving doses of 40, 80 and 120 mg, respectively, compared to no patients in the placebo group. Caution is advised in the use of FETZIMA in patients prone to obstructive urinary disorders. If symptoms of urinary hesitation, urinary retention, or dysuria develop during treatment with FETZIMA, consideration should be given to the possibility that they might be drug-related, and discontinuation or other appropriate medical intervention should be considered.

5.8 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.

5.9 Seizures

FETZIMA has not been systematically evaluated in patients with a seizure disorder. Patients with a history of seizures were excluded from clinical studies. FETZIMA should be prescribed with caution in patients with a seizure disorder. One case of seizure has been reported in pre-marketing clinical studies with FETZIMA.

5.10 Discontinuation Syndrome

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. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, consider resuming the previously prescribed dose. Subsequently, the dose may be decreased, but at a more gradual rate *[see Dosage and Administration (2.4)]*.

5.11 Hyponatremia

Although no adverse events of hyponatremia were reported for FETZIMA-treated patients in the clinical studies, hyponatremia has occurred 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. FETZIMA should be discontinued 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.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label.

- Hypersensitivity *[see Contraindications (4)]*
- Suicidal Thoughts and Behaviors in Adolescents and Young Adults *[see Warnings and Precautions (5.1)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.2)]*
- Elevated Blood Pressure *[see Warnings and Precautions (5.3)]*
- Elevated Heart Rate *[see Warnings and Precautions (5.4)]*
- Abnormal Bleeding *[see Warnings and Precautions (5.5)]*
- Angle Closure Glaucoma [*see Warnings and Precautions (5.6)]*

- Urinary Hesitation or Retention *[see Warnings and Precautions (5.7)]*
- Activation of Mania/Hypomania *[see Warnings and Precautions (5.8)]*
- Seizure [*see Warnings and Precautions (5.9)*]
- Discontinuation Syndrome *[see Warnings and Precautions (5.10)]*
- Hyponatremia *[see Warnings and Precautions (5.11)]*

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

Patient exposure

The safety of FETZIMA was evaluated in 2,673 patients (18-78 years of age) diagnosed with MDD who participated in clinical studies, representing 942 patient-years of exposure. Among the 2,673 FETZIMA-treated patients, 1,583 were exposed to FETZIMA in short-term, placebo-controlled studies. There were 825 patients who continued from short-term studies into a one-year, open-label extension study.

Of the 2,673 patients exposed to at least one dose of FETZIMA, 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.

Adverse reactions 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 reaction leading to discontinuation in at least 1% of the FETZIMA-treated patients in the short-term placebo-controlled studies was nausea (1.5%).

Common adverse reactions in placebo-controlled MDD studies

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, constipation, hyperhidrosis, heart rate increased, erectile dysfunction, tachycardia, vomiting, and palpitations.

Table 3 shows the incidence of adverse reactions that occurred in ≥ 2% of FETZIMA-treated MDD patients and at least twice the rate of placebo in the placebo-controlled studies.

Table 3 Adverse Reactions Occurring in ≥ 2% of FETZIMA-treated Patients and at Least Twice the rate of Placebo-treated Patients

System Organ Class ***Preferred Term***	***Placebo*** ***(N =1040)*** ***%***	***FETZIMA*** ***40-120 mg/d*** ***(N = 1583)*** ***%***

Gastrointestinal disorders		
Nausea	6	17
Constipation	3	9
Vomiting	1	5
Cardiac disorders		
Tachycardia[a]	2	6
Palpitations	1	5
Reproductive system and breast disorders[b]		
Erectile dysfunction[c]	1	6
Testicular pain[d]	<1	4
Ejaculation disorder[e]	<1	5
Investigations		
Heart rate increased[f]	1	6
Blood pressure increased[g]	1	3
Renal and urinary disorders		
Urinary hesitation	0	4
Skin and subcutaneous tissue disorders		
Hyperhidrosis	2	9
Rash[h]	0	2
Vascular disorders		
Hot flush	1	3
Hypotension[i]	1	3
Hypertension[j]	1	3
Metabolism and nutrition disorders		
Decreased appetite	1	3

[a] Tachycardia also includes: sinus tachycardia and postural orthostatic tachycardia syndrome
[b] Percentage is relative to the number of patients in the associated demographic sex category. Fewer than 2% of FETZIMA-treated MDD female patients in placebo-controlled clinical studies reported adverse events related to sexual function.
[c] erectile dysfunction includes: erectile dysfunction, organic erectile dysfunction and psychogenic erectile dysfunction
[d] testicular pain includes: testicular pain, epididymitis, and seminal vesiculitis
[e] ejaculation disorder includes: ejaculation disorder, ejaculation delayed, ejaculation failure, and premature ejaculation
[f] Heart rate increased also includes: orthostatic heart rate response increased
[g] Blood pressure increased also includes: blood pressure systolic increased, blood pressure diastolic increased and blood pressure orthostatic increased
[h] Rash also includes: rash generalized, rash maculo-papular, rash erythematous and rash macular
[i] Hypotension also includes: orthostatic hypotension and dizziness postural
[j] Hypertension also includes: labile hypertension
N = number of patients in the Safety Population

Dose-related adverse reactions

In pooled data from the short-term placebo-controlled fixed-dose studies, there were no dose-related adverse reactions (greater than 2% overall incidence) in patients treated with FETZIMA across the dose range 40-120 mg once daily, with the exception of erectile dysfunction and urinary hesitation (see Table 4).

Table 4 Dose-Related Adverse Reactions

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

[a] Percentage is relative to the number of male patients.
N = number of patients in the Safety Population

Other adverse reactions observed in clinical studies

Other infrequent adverse reactions, not described elsewhere in the label, occurring at an incidence of < 2% in MDD patients treated with FETZIMA were:

Cardiac disorders: Angina pectoris; Supraventricular and Ventricular extrasystoles

Eye disorders: Dry eye; Vision blurred; Conjunctival hemorrhage

General disorders: Chest pain; Thirst

Gastrointestinal disorders: Abdominal pain; Flatulence

Investigations disorders: Blood cholesterol increased; Liver function test abnormal

Nervous System disorders: Migraine; Paraesthesia; Syncope; Extrapyramidal disorder

Psychiatric disorders: Agitation; Anger; Bruxism; Panic attack; Tension; Aggression

Renal and Urinary disorder: Pollakiuria; Hematuria; Proteinuria

Respiratory, thoracic and mediastinal disorders: Yawning

Skin and subcutaneous tissue disorders: Dry skin; Pruritus; Urticaria

6.2 Postmarketing Experience

Besides these reactions reported under treatment with FETZIMA, other potentially severe adverse events have been reported from the post-marketing experience with milnacipran. Since levomilnacipran is the principal pharmacologically active component of milnacipran, one should take into account the fact that the following adverse event could also potentially occur under treatment with FETZIMA.

This adverse reaction includes: Takotsubo cardiomyopathy.

7 DRUG INTERACTIONS

Other than CYP3A4 drug interactions, FETZIMA is predicted, based on *in vitro* studies, to have a low potential to be involved in clinically significant pharmacokinetic drug interactions.

7.1 Monoamine Oxidase Inhibitors (MAOIs)

[see Dosage and Administration (2.5, 2.6), Contraindications (4), and Warnings and Precautions (5.2)]

7.2 Serotonergic Drugs

[see Dosage and Administration (2.5, 2.6), Contraindications (4), and Warnings and Precautions (5.2)]

7.3 Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of 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. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs 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 (5.5)]*.

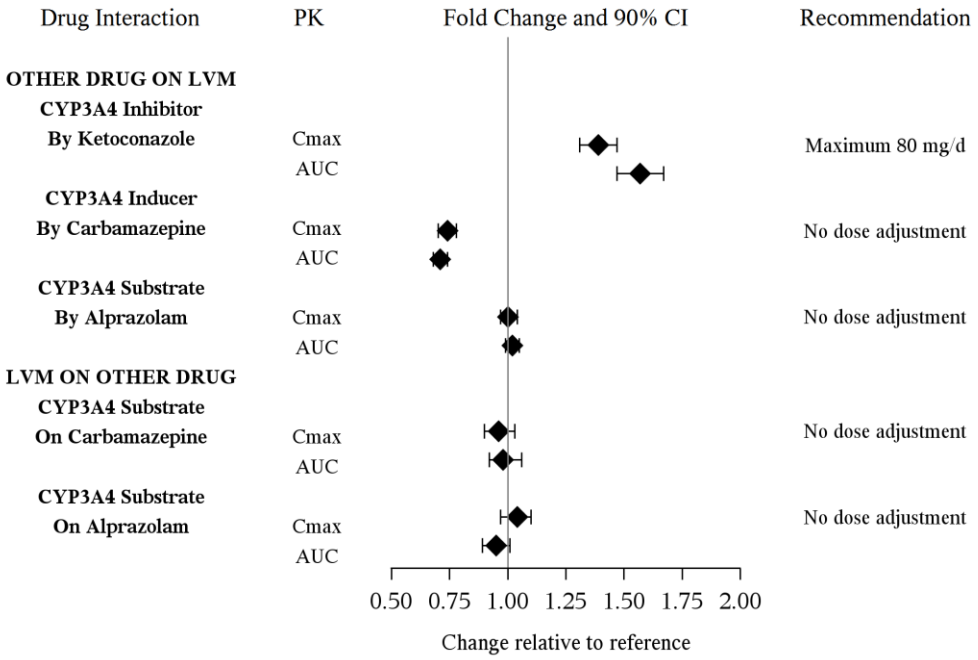
7.4 Potential for Other Drugs to Affect FETZIMA

Dose adjustment is recommended when FETZIMA is co-administered with strong inhibitors of CYP3A4 (e.g. ketoconazole) *[see Dosage and Administration (2.7)]*. An *in vivo* study showed a clinically meaningful increase in levomilnacipran exposure when FETZIMA was co-administered with the CYP3A4 inhibitor ketoconazole (see Figure 1).

No dose adjustment of FETZIMA is needed when co-administered with a CYP3A4 inducer or substrate. *In vivo* studies showed no clinically meaningful change in levomilnacipran exposure when co-administered with the CYP3A4 inducer carbamazepine or the CYP3A4 substrate alprazolam (see Figure 1).

No dose adjustment of FETZIMA is needed when co-administered with inhibitors of CYP2C8 , CYP2C19, CYP2D6, CYP2J2, P-glycoprotein, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2. *In vitro* studies suggested that CYP2C8, CYP2C19, CYP2D6, and CYP2J2 had minimal contributions to metabolism of levomilnacipran. In addition, levomilnacipran is not a substrate of BCRP, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2 and is a weak substrate of P-gp.

Figure 1 PK Interactions between Levomilnacipran (LVM) and Other Drugs



7.5 Potential for FETZIMA to Affect Other Drugs

No dose adjustment of the concomitant medication is recommended when FETZIMA is administered with a substrate of CYP3A4, CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, P-gp, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2. *In vitro* studies have shown that levomilnacipran is not an inhibitor of CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, P-gp, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2. Concomitant use of FETZIMA with alprazolam or carbamazepine, substrates of CYP3A4, had no significant effect on alprazolam or carbamazepine plasma concentrations (see Figure 1).

7.6 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, including those with a similar mechanism of action.

Alcohol

In an *in vitro* study, alcohol interacted with the extended-release properties of FETZIMA. If FETZIMA is taken with alcohol, a pronounced accelerated drug release may occur. It is recommended that FETZIMA extended-release capsules not be taken with alcohol.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies of FETZIMA in pregnant women. Neonates exposed to dual reuptake inhibitors of serotonin and norepinephrine (such as FETZIMA), or selective serotonin reuptake inhibitors late in the third trimester have developed complications that can arise immediately upon delivery. Levomilnacipran was not teratogenic in rats or rabbits when given during the period of organogenesis at doses up to 8 or 16 times the maximum recommended human dose (MRHD) of 120 mg on a mg/m2 basis, respectively. However, an increase in early post natal rat pup mortality was seen at a dose equivalent to 5 times the MRHD given during pregnancy and lactation. FETZIMA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

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 (5.2)]*.

A prospective longitudinal study of 201 women with history of major depression who were euthymic at the beginning of pregnancy, showed women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

Animal Data

No teratogenic effects were observed when levomilnacipran was administered to pregnant rats or rabbits during the period of organogenesis at oral doses up to 100 mg/kg/day. This dose is 8 and 16 times (in rats and rabbits, respectively) the maximum recommended human dose (MRHD) of 120 mg on a mg/m2 basis. Fetal body weights were reduced in rats, and skeletal ossification was delayed in both rats and rabbits at this dose; these effects were not observed in either species at doses up to 30 mg/kg/day, 2.4 times the MRHD in rats or 5 times the MRHD in rabbits.

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. 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.

8.3 Nursing Mothers

It is not known if FETZIMA is present in human milk. Studies have shown that levomilnacipran is present in 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.

8.4 Pediatric Use

Clinical studies on the use of 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 Boxed Warning and Warnings and Precautions (5.1)]*.

8.5 Geriatric Use

No dose adjustment is recommended on the basis of age (see Figure 2). 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).

Of the total number of subjects in clinical studies of FETZIMA, 2.8% of patients were age 65 or older.

Because levomilnacipran is predominately excreted by the kidney, renal clearance of levomilnacipran should be considered when determining the dose *[see Dosage and Administration (2.3)]*.

SSRIs and SNRIs, including FETZIMA, 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 (5.11)]*.

8.6 Hepatic Impairment

Hepatic elimination of levomilnacipran is low. Dose adjustment is not recommended in subjects with mild (Child-Pugh score of 1-6), moderate (Child-Pugh score of 7-9), or severe (Child-Pugh score of 10-13) hepatic impairment (see Figure 2).

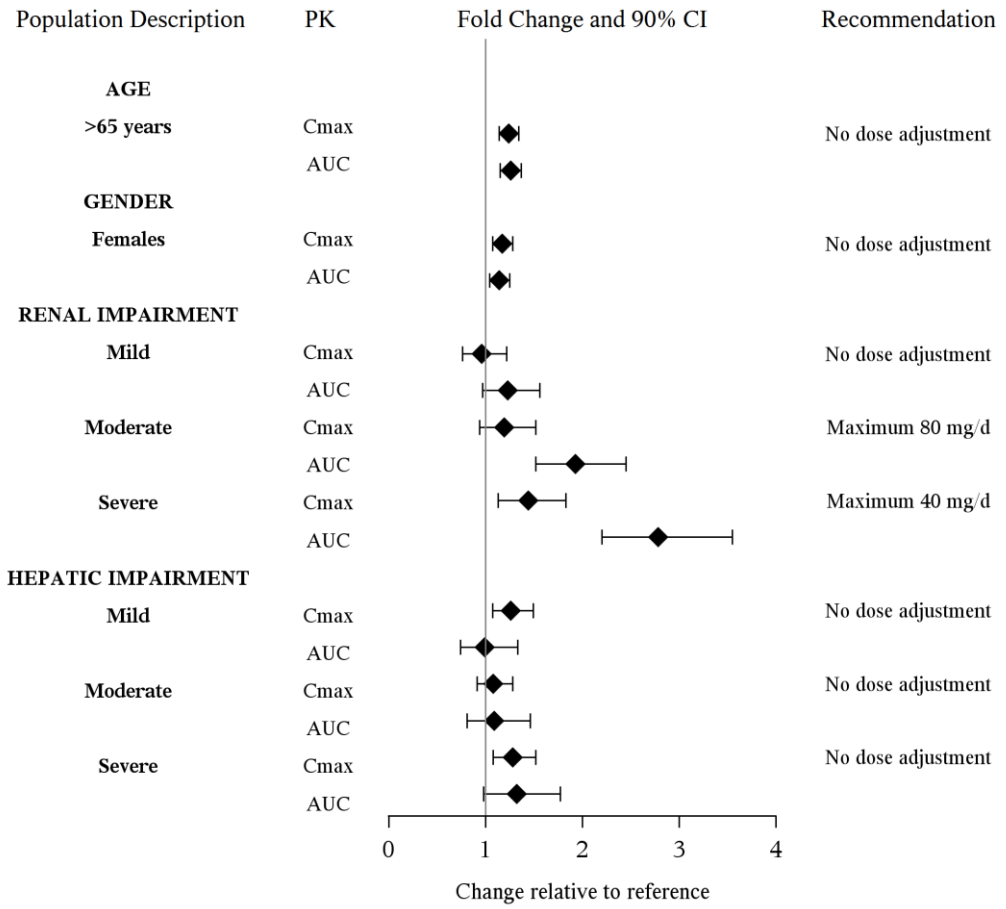
8.7 Renal Impairment

Renal excretion plays a predominant role in the elimination of levomilnacipran. Dose adjustment is not recommended for patients with mild (creatinine clearance of 60-89 ml/min) renal impairment. Dosing adjustment is recommended for patients with moderate (creatinine clearance of 30-59 ml/min) or severe (creatinine clearance of 15-29 ml/min) renal impairment (see Figure 2). FETZIMA is not recommended for patients with end stage renal disease *[see Dosage and Administration (2.3)]*.

8.8 Gender

Dose adjustment based on gender is not recommended (see Figure 2).

Figure 2 Effect of Intrinsic Factors on Levomilnacipran PK



The data shown for elderly subjects (>65 years) are relative to younger subjects (18-45 years).
The data shown for female subjects are relative to male subjects.
The data shown for renal and hepatic impairment are relative to subjects with normal renal and hepatic function, respectively.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

FETZIMA is not a controlled substance.

9.2 Abuse

FETZIMA has not been systematically studied in animals or humans for its potential for abuse. 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).

9.3 Dependence

FETZIMA has not been systematically studied in animals or humans for its potential for dependence.

10 OVERDOSAGE

10.1 Human Experience

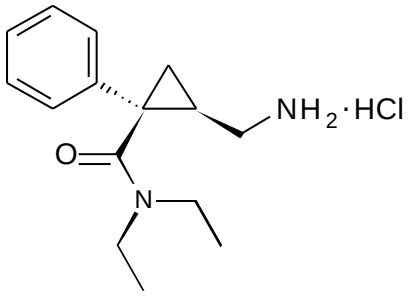
There is limited clinical experience with FETZIMA overdose in humans. In clinical studies, cases of ingestions up to 360 mg daily were reported with none being fatal.

10.2 Management of Overdose

No specific antidotes for FETZIMA are known. In managing overdose, provide supportive care, including close medical supervision and monitoring, and consider the possibility of multiple drug involvement. In case of an overdose, consult a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice. The high volume of distribution of levomilnacipran suggests that dialysis will not be effective in reducing levomilnacipran plasma concentrations.

11 DESCRIPTION

The active ingredient of FETZIMA is levomilnacipran, which is a selective serotonin and norepinephrine reuptake inhibitor (SNRI). The chemical name of levomilnacipran is (1S,2R)-2-(aminomethyl)-N,N-diethyl-1-phenylcyclopropanecarboxamide hydrochloride; its empirical formula is $C_{15}H_{23}ClN_2O$ and its molecular weight is 282.8 g/mol. Levomilnacipran (Initial US approval: 2013) is the 1S,2R-enantiomer of milnacipran. The chemical structure is:



FETZIMA capsules are intended for oral administration only. Each FETZIMA capsule contains extended-release beads with 23.0, 45.9, 91.8, or 137.8 mg of levomilnacipran hydrochloride equivalent to 20, 40, 80, or 120 mg of levomilnacipran, respectively. Inactive ingredients include sugar spheres, ethylcellulose, talc, povidone, triethyl citrate, hypromellose, and titanium dioxide. Inactive ingredients also include shellac glaze, black iron oxide, yellow iron oxide (20 mg and 40 mg capsules only), and red iron oxide (80 mg and 120 mg capsules only).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The exact mechanism of the antidepressant action of levomilnacipran is unknown, but is thought to be related to the potentiation of serotonin and norepinephrine in the central nervous system,

through inhibition of reuptake at serotonin and norepinephrine transporters. Non-clinical studies have shown that levomilnacipran is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI).

12.2 Pharmacodynamics

Levomilnacipran binds with high affinity to the human serotonin (5-HT) and norepinephrine (NE) transporters (Ki = 11 and 91 nM, respectively) and potently inhibits 5-HT and NE reuptake (IC50 = 16-19 and 11 nM, respectively). Levomilnacipran lacks significant affinity for any other receptors, ion channels or transporters tested *in vitro*, including serotonergic (5HT1-7), α- and β-adrenergic, muscarinic, or histaminergic receptors and Ca2+, Na+, K+ or Cl- channels. Levomilnacipran did not inhibit monoamine oxidase (MAO).

Cardiovascular Electrophysiology

At a dose 2.5 times the maximum recommended dose, levomilnacipran does not prolong QTc to any clinically relevant extent.

12.3 Pharmacokinetics

The concentration of levomilnacipran at steady state is proportional to dose when administered from 25 to 300 mg once daily. Following an oral administration, the mean apparent total clearance of levomilnacipran is 21-29 L/h. Steady-state concentrations of levomilnacipran are predictable from single-dose data. The apparent terminal elimination half-life of levomilnacipran is 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. Interconversion between levomilnacipran and its stereoisomer does not occur in humans.

Absorption

The relative bioavailability of levomilnacipran after administration of FETZIMA ER was 92% when compared to oral solution. Levomilnacipran concentration was not significantly affected when FETZIMA was administered with food.

The median time to peak concentration (Tmax) of levomilnacipran is 6-8 hours after oral administration.

Distribution

Levomilnacipran is widely distributed with an apparent volume of distribution of 387-473 L; plasma protein binding is 22% over concentration range of 10 to 1000 ng/mL.

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 [*see Drug Interactions (7.4, 7.5)]*.

Elimination/Excretion

Levomilnacipran and its metabolites are eliminated primarily by renal excretion. Following oral administration of 14C-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 *[see Dosage and Administration (2.3)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Levomilnacipran administered by oral gavage to rats for 2 years and Tg.rasH2 mice for 6 months did not increase the incidence of tumors in either study.

Rats received levomilnacipran at doses up to 90/70 mg/kg/day (the dose was lowered in males after 45 weeks of dosing). The 90 mg/kg/day dose is 7 times the maximum recommended human dose (MRHD) of 120 mg on a mg/m2 basis.

Tg.rasH2 mice received levomilnacipran at doses up to 150 mg/kg/day. This dose is 6 times the MRHD.

Mutagenesis

Levomilnacipran was not mutagenic in the *in vitro* bacterial mutation assay (Ames test) and was not clastogenic in an *in vivo* micronucleus assay in rats. Additionally, levomilnacipran was not genotoxic in the *in vitro* mouse lymphoma (L5178Y TK+/-) cell forward mutation assay.

Impairment of Fertility

When levomilnacipran was administered orally to male and female rats before mating, through mating and up to Day 7 of gestation at doses up to 100 mg/kg/day, no effects were observed on fertility. This dose is 8 times the MRHD.

14 CLINICAL STUDIES

14.1 Treatment of Major Depressive Disorder

The efficacy of FETZIMA for the treatment of major depressive disorder (MDD) was established in three 8-week randomized, double-blind, placebo-controlled studies (at doses 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. Two of the studies were fixed dose (Study 1 and Study 2) and one study was flexible dose (Study 3).

In Study 1, patients received 40 mg (n = 178), 80 mg (n = 179), or 120 mg (n = 180) of FETZIMA once daily, or placebo (n = 176). In Study 2, patients received either 40 mg (n = 188) or 80 mg (n = 188) of FETZIMA once daily, or placebo (n = 186). In the flexible-dose study (Study 3), patients received 40 to 120 mg (n = 217) of FETZIMA once daily, or placebo (n =

Serotonin Syndrome

Caution patients about the risk of serotonin syndrome, particularly with the concomitant use of FETZIMA and triptans, tramadol, amphetamines, tryptophan supplements, other serotonergic agents, or antipsychotic drugs *[see Warnings and Precautions (5.2) and Drug Interactions (7.2)]*.

Effect on Blood Pressure and Heart Rate

Advise patients that they should have regular monitoring of blood pressure and heart rate when taking FETZIMA *[see Warnings and Precautions (5.3, 5.4)]*.

Abnormal Bleeding

Caution patients about the concomitant use of FETZIMA and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of abnormal bleeding *[see Warnings and Precautions (5.5)]*.

Angle Closure Glaucoma

Patients should be advised that taking FETZIMA can cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle closure glaucoma. Pre-existing glaucoma is almost always open-angle glaucoma because angle closure glaucoma, when diagnosed, can be treated definitively with iridectomy. Open-angle glaucoma is not a risk factor for angle closure glaucoma. Patients may wish to be examined to determine whether they are susceptible to angle closure, and have a prophylactic procedure (e.g., iridectomy), if they are susceptible *[see Warnings and Precautions (5.6)]*.

Urinary Hesitation or Retention

Caution patients about the risk of urinary hesitation and retention while taking FETZIMA, particularly in patients prone to obstructive urinary disorders *[see Warnings and Precautions (5.7)]*.

Activation of Mania/Hypomania

Advise patients and their caregivers to observe for signs of activation of mania/hypomania *[see Warnings and Precautions (5.8)]*.

Seizures

Caution patients about using FETZIMA if they have a history of a seizure disorder *[see Warnings and Precautions (5.9)]*. Patients with a history of seizures were excluded from clinical studies.

Discontinuation Syndrome

Advise patients not to stop taking FETZIMA without first talking with their healthcare provider. Patients should be aware that discontinuation effects may occur when suddenly stopping FETZIMA *[see Warnings and Precautions (5.10)]*.

Hyponatremia

Advise patients that if they are treated with diuretics, or are otherwise volume depleted, or are elderly, they may be at greater risk of developing hyponatremia while taking FETZIMA *[see Warnings and Precautions (5.11)]*.

Alcohol

Advise patients to avoid consumption of alcohol while taking FETZIMA *[see Drug Interactions (7.6)]*.

Allergic Reactions

Advise patients to notify their healthcare provider if they develop an allergic reaction such as rash, hives, swelling, or difficulty breathing.

Pregnancy

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during therapy with FETZIMA *[see Use in Specific Populations (8.1)]*.

Nursing Mothers

Advise patients to notify their healthcare provider if they are breastfeeding an infant and would like to continue or start FETZIMA *[see Use in Specific Populations (8.3)]*.

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.

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MEDICATION GUIDE

FETZIMA® (fet-ZEE-muh)
(levomilnacipran)
extended-release capsules

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

Talk to your healthcare provider about:

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

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

FETZIMA and other antidepressant medicines may cause serious side effects.

1. **Depression or other serious mental illnesses are the most important causes of suicidal thoughts or actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness).
2. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, or young adults within the first few months of treatment.**

   FETZIMA is not approved for use in children. Talk to your child's healthcare provider for more information.
3. **How can I watch for and try to prevent suicidal thoughts and actions?**

   - Pay close attention to any changes in mood, behavior, thoughts, or feelings, especially sudden changes. This is very important when an antidepressant medicine is started or when the dose is changed.
   - Call your healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
   - Keep all follow-up visits with your healthcare provider as scheduled. Call your healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call your healthcare provider right away if you have any of the following symptoms or feelings, especially if they are new, worse, or worry you:

- attempts to commit suicide
- acting on dangerous impulses
- acting aggressive, being angry, or violent

Who should not take FETZIMA?

Do not take FETZIMA if you:

- are allergic to levomilnacipran, milnacipran HCl, or any of the ingredients in FETZIMA. See the end of this Medication Guide for a complete list of 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 or intravenous methylene blue.
- have taken an MAOI within 14 days unless directed by your healthcare provider

What should I tell my healthcare provider before taking FETZIMA?

Before you take FETZIMA, tell your healthcare provider if you:

- have high blood pressure
- have heart problems
- have or had bleeding problems
- have or had urinary retention or problems urinating
- have mania or bipolar disorder (manic depression)
- have or had seizures or convulsions
- have low salt (sodium) levels in your blood
- have kidney problems
- drink alcohol
- are pregnant or plan to become pregnant. It is not known if FETZIMA will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if FETZIMA passes into breast milk. Talk to your healthcare provider if you are or plan to breast feed your baby while taking FETZIMA.

Tell your healthcare provider about all the medicines that you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Especially tell your healthcare provider if you take:

- medicines used to treat migraine headache (triptans)
- medicines used to treat mood, anxiety, psychotic or thought disorders, including tricyclics, lithium, fentanyl, tryptophan, selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), buspirone, amphetamines, or antipsychotics
- sibutramine
- tramadol
- over-the-counter supplements such as tryptophan or St. John's Wort
- nonsteroidal anti-inflammatory drugs (NSAIDS)
- aspirin
- warfarin (Coumadin®, Jantoven®)
- diuretics

Ask your healthcare provider if you are not sure if you are taking any of these medicines.

Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get new medicine.

FETZIMA and some medicines may affect each other, may not work as well, or may cause serious side effects when taken together.

How should I take FETZIMA?

- Take FETZIMA exactly as your healthcare provider tells you to take it.
- Take FETZIMA at about the same time each day.
- Your healthcare provider may need to change the dose of FETZIMA until it is the right dose for you.
- Do not start or stop taking FETZIMA without talking to your healthcare provider first. Stopping FETZIMA suddenly can cause side effects.
- FETZIMA may be taken with or without food.
- Swallow FETZIMA whole. Do not chew, crush, or cut FETZIMA.
- If you miss a dose of FETZIMA, take the missed dose as soon as you remember. If it is almost time for the next dose, skip the missed dose and take your next dose at the regular time. Do not take two doses of FETZIMA at the same time.
- If you take too much FETZIMA, call your healthcare provider or your poison control center at 1-800-222-1222, or go to the nearest hospital emergency room right away.

What should I avoid while taking FETZIMA?

- FETZIMA can cause sleepiness or may affect your ability to make decisions, think clearly, or react quickly. You should not drive, operate heavy machinery, or do other dangerous activities until you know how FETZIMA affects you.
- You should not drink alcohol while taking FETZIMA. See "**What should I tell my healthcare provider before taking FETZIMA?**"

What are the possible side effects of FETZIMA?

FETZIMA may cause serious side effects, including:

1. **high blood pressure** (hypertension). Your healthcare provider should evaluate your blood pressure before and while you are taking FETZIMA. If you have high blood pressure, it should be controlled before you start taking FETZIMA.

2. **increased heart rate (palpitations).** Your healthcare provider should evaluate your heart rate before and while you are taking FETZIMA.

3. **abnormal bleeding or bruising.** FETZIMA may increase your risk of bleeding or bruising, especially if you take the blood thinner warfarin (Coumadin®, Jantoven®), a non-steroidal anti-inflammatory drug (NSAID), or aspirin.

4. **visual problems**
   - eye pain
   - changes in vision

- swelling or redness in or around eye

Only some people are at risk for these problems. You may want to undergo an eye examination to see if you are at risk and receive preventative treatment if you are.

5. **urinary hesitation and retention** (difficulty urinating or unable to urinate)

6. **hypomania** (manic episodes). Symptoms of manic episodes include:
   - greatly increased energy
   - severe problems sleeping
   - racing thoughts
   - reckless behavior
   - unusually grand ideas
   - excessive happiness or irritability
   - talking more or faster than usual

7. **seizures or convulsions**

8. **discontinuation symptoms:** Do not stop 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

9. **low levels of salt (sodium) in your blood**. Symptoms of this may include: headache, difficulty concentrating, memory changes, confusion, weakness and unsteadiness on your feet. Symptoms of severe or sudden cases of low salt levels in your blood may include: hallucinations (seeing or hearing things that are not real), fainting, seizures and coma. If not treated, severe low sodium levels could cause death.

The most common side effects of FETZIMA include:

- nausea or vomiting
- constipation
- sweating
- erectile dysfunction

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of FETZIMA. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store FETZIMA?

Store FETZIMA at room temperature between 68°F to 77°F (20°C to 25°C).
Keep FETZIMA and all medicines out of the reach of children.

General information about the safe and effective use of FETZIMA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use FETZIMA for a condition for which it was not prescribed. Do not give FETZIMA to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about FETZIMA. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider or pharmacist for information about FETZIMA that is written for healthcare professionals.

For more information, go to www.FETZIMA.com or call 1-800-678-1605.

What are the ingredients in FETZIMA?

Active ingredient: levomilnacipran hydrochloride

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

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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