

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 thoughts and behavior in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors (5.1). FETZIMA is not approved for use in pediatric patients (8.4).

RECENT MAJOR CHANGES

Warnings and Precautions (5.12) 9/2021

INDICATIONS AND USAGE

FETZIMA is a serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for the treatment of Major Depressive Disorder (MDD) in adults (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

- **Serotonin Syndrome:** Increased risk when co-administered with other serotonergic agents (e.g., SSRI, SNRI, triptans), but also when taken alone. If it occurs, discontinue FETZIMA and initiate supportive treatment (5.2).
- **Elevated Blood Pressure and Heart Rate:** Control hypertension before initiating therapy with FETZIMA. Monitor blood pressure regularly during treatment (5.3, 5.4).
- **Increased Risk of Bleeding:** Concomitant use of NSAIDs, aspirin, other antiplatelet drugs, warfarin, and other anticoagulants may increase this risk (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).
- **Sexual Dysfunction:** Fetzima may cause symptoms of sexual dysfunction (5.12).

ADVERSE REACTIONS

The most common adverse reactions (incidence \geq 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:** Third trimester use may increase risk for symptoms of poor adaptation (respiratory distress, temperature instability, feeding difficulty, hypotonia, tremor, irritability) in the neonate. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

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FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors [*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[®] is indicated for the treatment of major depressive disorder (MDD) in adults [*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 Screen for Bipolar Disorder Prior to Starting FETZIMA

Prior to initiating treatment with FETZIMA or another antidepressant, screen patients for a personal or family history of bipolar disorder, mania, or hypomania [*see Warnings and Precautions (5.8)*].

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* (7.1)]

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 Adolescents and Young Adults

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with MDD. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 1.

Table 1: Risk Differences of the Number of Patients of Suicidal Thoughts and Behavior in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric and Adult Patients

| Age Range | Drug-Placebo Difference in Number of Patients of Suicidal Thoughts or Behaviors per 1000 Patients Treated |
|-----------------|---|
| | Increases Compared to Placebo |
| <18 years old | 14 additional patients |
| 18-24 years old | 5 additional patients |
| | Decreases Compared to Placebo |
| 25-64 years old | 1 fewer patient |
| ≥65 years old | 6 fewer patients |

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with MDD that antidepressants

delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors.

Monitor all antidepressant-treated patients for any indication for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy, and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing FETZIMA, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

5.2 Serotonin Syndrome

Selective-serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), including FETZIMA, can precipitate serotonin syndrome, a potentially life-threatening condition. The risk is increased with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's Wort) and with drugs that impair metabolism of serotonin, i.e., MAOIs [*see Contraindications (4), Drug Interactions (7.1)*]. Serotonin syndrome can also occur when these drugs are used alone.

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).

The concomitant use of FETZIMA with MAOIs is contraindicated. In addition, do not initiate FETZIMA in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection). If it is necessary to initiate treatment with a MAOI such as linezolid or intravenous methylene blue in a patient taking FETZIMA, discontinue FETZIMA before initiating treatment with the MAOI [*see Dosage and Administration (2.5, 2.6) and Contraindications (4), Drug Interactions (7.1)*].

Monitor all patients taking FETZIMA for the emergence of serotonin syndrome. Discontinue treatment with FETZIMA and any concomitant serotonergic agents immediately if the above events occur and initiate supportive symptomatic treatment. If concomitant use of FETZIMA with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome and monitor for symptoms.

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

| | <i>Placebo</i> | <i>FETZIMA 40-120 mg/day</i> |
|---|----------------|----------------------------------|
| 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 \geq 140 mm Hg and an increase \geq 15 mm Hg OR DBP \geq 90 mm Hg and an increase \geq 10 mm Hg for at least 3 consecutive visits | 1.2 | 1.8 |
| Strict Criteria: SBP \geq 140 mm Hg and an increase \geq 15 mm Hg AND DBP \geq 90 mm Hg and an increase \geq 10 mm Hg for at least 3 consecutive visits | 0.1 | 0.3 |
| Upward Shifts in Hypertensive Status ^a , % of patients | | |
| Normal/ Pre-hypertensive \rightarrow Stage I/ Stage II | 7.1 | 10.4 |

^a Normal Blood Pressure: SBP < 120 mm Hg **and** DBP < 80 mm Hg
Pre-hypertension: SBP \geq 120 mm Hg **and** \leq 139 mm Hg or DBP \geq 80 mm Hg **and** \leq 89 mm Hg
Stage I hypertension: SBP \geq 140 mm Hg **and** \leq 159 mm Hg or DBP \geq 90 mm Hg **and** \leq 99 mm Hg
Stage II hypertension: SBP \geq 160 mm Hg **or** DBP \geq 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 \geq 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 Increased Risk of Bleeding

Drugs that interfere with serotonin reuptake, 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.

Inform patients about the risk of bleeding associated with the concomitant use of FETZIMA and NSAIDs, aspirin, or other drugs that affect coagulation [*see Drug Interactions (7.1)*].

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.

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.

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

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including FETZIMA. 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.

5.12 Sexual Dysfunction

Use of SNRIs, including Fetzima, may cause symptoms of sexual dysfunction [*see Adverse Reactions (6.1)*]. In male patients, SNRI use may result in ejaculatory delay or failure, decreased libido, and erectile dysfunction. In female patients, SNRI use may result in decreased libido and delayed or absent orgasm.

It is important for prescribers to inquire about sexual function prior to initiation of Fetzima and to inquire specifically about changes in sexual function during treatment, because sexual function may not be spontaneously reported. When evaluating changes in sexual

function, obtaining a detailed history (including timing of symptom onset) is important because sexual symptoms may have other causes, including the underlying psychiatric disorder. Discuss potential management strategies to support patients in making informed decisions about treatment.

6 ADVERSE REACTIONS

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)*]
- Increased Risk of 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)*]
- Sexual Dysfunction [*see Warnings and Precautions (5.12)*]

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 3,317 patients (18-78 years of age) diagnosed with MDD who participated in clinical studies, representing 1,186 patient-years of exposure. Among the 3,317 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 3,317 patients exposed to at least one dose of FETZIMA, 895 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 $\geq 5\%$ 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 $\geq 2\%$ of FETZIMA-treated MDD patients and at least twice the rate of placebo in the placebo-controlled studies.

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

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

| <i>System Organ Class Preferred Term</i> | <i>Placebo (N = 362) %</i> | <i>FETZIMA</i> | | |
|--|------------------------------------|------------------------------------|------------------------------------|-------------------------------------|
| | | <i>40 mg/d (N = 366) %</i> | <i>80 mg/d (N = 367) %</i> | <i>120 mg/d (N = 180) %</i> |
| 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; Extrapyrarnidal 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

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

Cardiac disorders: Takotsubo cardiomyopathy

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with FETZIMA

Table 5 includes clinically important drug interactions with FETZIMA.

Table 5: Clinically Important Drug Interactions with FETZIMA

| Monoamine Oxidase Inhibitors (MAOIs) | |
|---|---|
| <i>Clinical Impact:</i> | Concomitant use of SSRIs and SNRIs including FETZIMA with MAOIs increases the risk of serotonin syndrome. |
| <i>Intervention:</i> | <p>Concomitant use of FETZIMA is contraindicated:</p> <ul style="list-style-type: none"> • With an MAOI intended to treat psychiatric disorders or within 7 days of stopping treatment with FETZIMA. • Within 14 days of stopping an MAOI intended to treat psychiatric disorders • In a patient who is being treated with linezolid or intravenous methylene blue <p>[see Dosage and Administration (2.5, 2.6), Contraindications (4), and Warnings and Precautions (5.2)].</p> |
| <i>Examples:</i> | selegiline, tranylcypromine, isocarboxazid, phenelzine, linezolid, methylene blue |
| Other Serotonergic Drugs | |
| <i>Clinical Impact:</i> | Concomitant use of FETZIMA with other serotonergic drugs increases the risk of serotonin syndrome. |
| <i>Intervention:</i> | Monitor for symptoms of serotonin syndrome when FETZIMA is used concomitantly with other drugs that may affect the serotonergic neurotransmitter systems. If serotonin syndrome occurs, immediately discontinue FETZIMA and/or concomitant serotonergic drugs [see Dosage and Administration (2.5, 2.6), Contraindications (4), and Warnings and Precautions (5.2)]. |
| <i>Examples:</i> | other SNRIs, SSRIs, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, amphetamines, tryptophan, and St. John's Wort |
| Drugs that Interfere with Hemostasis | |
| <i>Clinical Impact:</i> | Concomitant use of FETZIMA with an antiplatelet or anticoagulant drug may potentiate the risk of bleeding. This may be due to the effect of FETZIMA on the release of serotonin by platelets. |

| | |
|---------------------------------|--|
| <i>Intervention:</i> | Closely monitor for bleeding for patients receiving an antiplatelet or anticoagulant drug when FETZIMA is initiated or discontinued [<i>see Warnings and Precautions (5.5)</i>]. |
| <i>Examples:</i> | NSAIDs, aspirin, and warfarin |
| Strong CYP3A4 Inhibitors | |
| <i>Clinical Impact:</i> | Concomitant use of FETZIMA with strong CYP3A4 inhibitors increases levomilnacipran exposure [<i>see Pharmacokinetics (12.3)</i>]. |
| <i>Intervention:</i> | The dose of FETZIMA should not exceed 80 mg once daily when used with strong CYP3A4 inhibitors [<i>see Dosage and Administration (2.7)</i>]. |
| <i>Examples:</i> | Ketoconazole, itraconazole, clarithromycin |
| Alcohol | |
| <i>Clinical Impact:</i> | Concomitant use of FETZIMA and alcohol may result in accelerated release of levomilnacipran. |
| <i>Intervention:</i> | Avoid concomitant use of FETZIMA and alcohol [<i>see Clinical Pharmacology (12.3)</i>]. |

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or visiting online at <https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/>.

Risk Summary

The available data on FETZIMA use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are risks associated with untreated depression in pregnancy and with exposure to SNRIs and SSRIs, including FETZIMA, during pregnancy (*see Clinical Considerations*).

In animal reproduction studies, levomilnacipran was not associated with malformations 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 (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Women who discontinued antidepressants during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressants. This finding is from a prospective, longitudinal study that followed 201 pregnant women with a history of major depressive disorder who were euthymic and taking antidepressants at the beginning of pregnancy. Consider the risk of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum.

Maternal adverse reactions

Use of SNRIs in late pregnancy may be associated with an increased risk of postpartum hemorrhage [see *Warnings and Precautions (5.5)*].

Fetal/Neonatal adverse reactions

Neonates exposed to SNRIs or SSRIs, including FETZIMA, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These findings are consistent with either direct toxic effect of SSRIs and SNRIs 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 and 5.10)*].

Data

Animal Data

No malformations 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 on a mg/m² basis.

When levomilnacipran was administered to pregnant rats at an oral dose of 60 mg/kg/day, 5 times the MRHD, during organogenesis and throughout pregnancy and lactation, there was an increase in early postnatal pup mortality; no pup mortality was seen at 20 mg/kg/day, 1.6 times the MRHD on a mg/m² basis. Among the surviving pups, pre- and post-weaning pup weight gain was reduced up to at least 8 weeks of age; however, physical and functional development, including reproductive performance of the progeny, was not affected. The effects on body weight gain were not seen at 7 mg/kg/day, 0.6 times the MRHD on a mg/m² basis.

8.2 Lactation

Risk Summary

There are no available data on the presence of levomilnacipran in human milk; however, racemic milnacipran is present in human milk (*see Data*). There are no reports on the effects of

levomilnacipran or milnacipran on the breastfed infant or the effects on milk production. However, there are reports of agitation, irritability, poor feeding and poor weight gain in infants exposed to SSRIs or SNRIs through breast milk (see Clinical Considerations). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for FETZIMA and any potential adverse effects on the breastfed child from FETZIMA or from the underlying maternal conditions.

Clinical Considerations

Infants exposed to FETZIMA should be monitored for agitation, irritability, poor feeding and poor weight gain.

Data

Milnacipran, a racemic mixture that contains levomilnacipran (the 1S,2R-enantiomer of milnacipran), is present in the milk of lactating women treated with milnacipran. In a lactation pharmacokinetic study with milnacipran, a single, oral dose of 50 mg milnacipran HCl tablet was administered to 8 lactating women who were at least 12 weeks postpartum and weaning their infants. The milk/plasma AUC ratio of milnacipran was 1.85 ± 0.38 . The maximum estimated weight-adjusted daily infant dose for milnacipran from breast milk (assuming mean milk consumption of 150 mL/kg/day) was 5% of the maternal weight-adjusted dose based on peak plasma concentrations.

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 the 8-week 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)*].

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

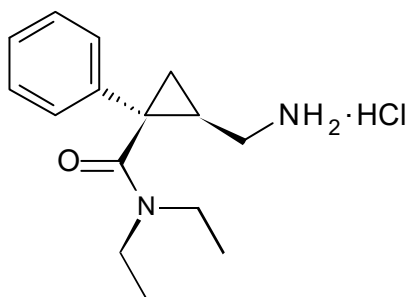
There is limited clinical experience with FETZIMA overdose in humans. In clinical studies, cases of ingestions up to 360 mg daily were reported with none being fatal.

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

Fetzima contains levomilnacipran hydrochloride, a selective serotonin and norepinephrine reuptake inhibitor (SNRI). The chemical name of levomilnacipran hydrochloride is (1S,2R)-2-(aminomethyl)-N,N-diethyl-1-phenylcyclopropanecarboxamide hydrochloride; its empirical formula is C₁₅H₂₃ClN₂O and its molecular weight is 282.8 g/mol. Levomilnacipran (Initial US approval: 2013) is the 1S,2R-enantiomer of milnacipran. The chemical structure of levomilnacipran hydrochloride is:



FETZIMA extended-release capsules are intended for oral administration. 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 ethylcellulose, hypromellose, povidone, sugar spheres, talc, titanium dioxide, and triethyl citrate. Inactive ingredients also include black iron oxide, red iron oxide (80 mg and 120 mg capsules only), shellac glaze, and yellow iron oxide (20 mg and 40 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 ($K_i = 11$ and 91 nM, respectively) and potently inhibits 5-HT and NE reuptake ($IC_{50} = 16-19$ 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 Ca^{2+} , 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 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 (T_{max}) 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.

Elimination

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.

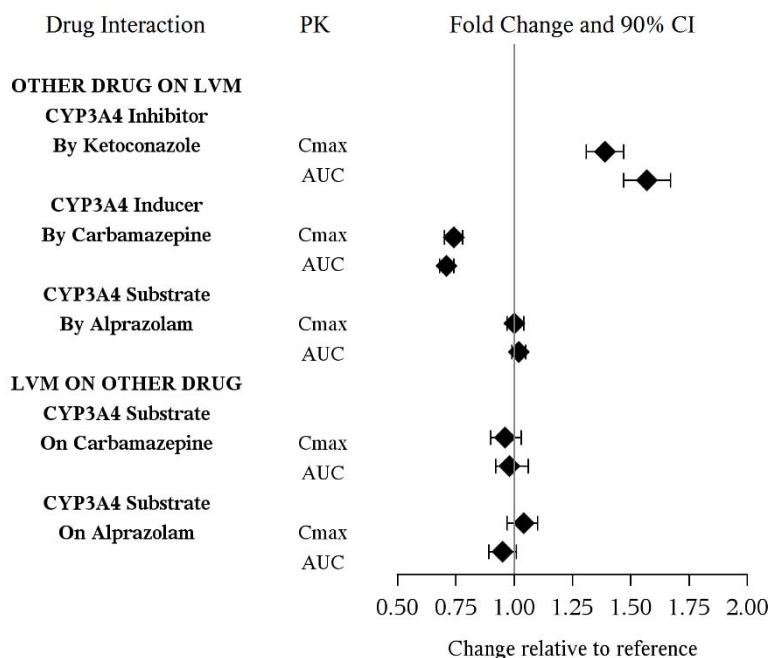
Excretion

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)*].

Drug Interaction Studies

The drug interaction studies for levomilnacipran are summarized in Figure 1.

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



In vitro Studies

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.

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.

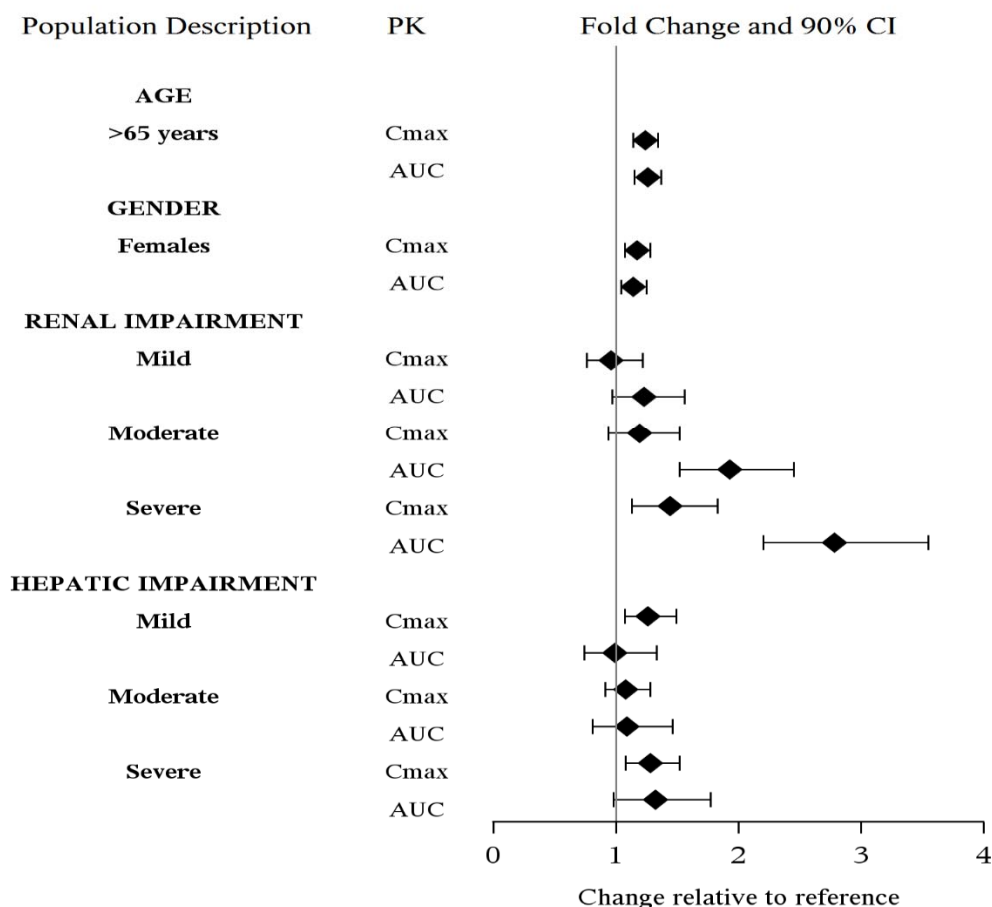
Alcohol

An *in vitro* study indicated increases of levomilnacipran release from Fetzima extended-release capsules (20, 40, 80, and 120 mg) at 2 hours by approximately 9.5%, 23% and 56% in the presence of 5%, 20% and 40% (v/v) alcohol, respectively. Effect of 40% alcohol resulted in nearly complete drug release in 4 hours. There is no *in vivo* study conducted for the effect of alcohol on drug exposure.

Special Populations

The effect of intrinsic patient factors on the pharmacokinetics of levomilnacipran is presented in Figure 2.

Figure 2 Effect of Intrinsic Factors on Levomilnacipran PK



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.

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 on a mg/m² basis.

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 = 217) with 21%, 34%, and 44% of FETZIMA patients on 40 mg, 80 mg, and 120 mg, respectively at the end of their treatment.

In all three studies, FETZIMA demonstrated superiority over placebo in the improvement of depressive symptoms as measured by the Montgomery-Asberg Depression Rating Scale (MADRS) total score (see Table 6). FETZIMA also demonstrated superiority over placebo as measured by improvement in the Sheehan Disability Scale (SDS) functional impairment total score.

Table 6 Summary of Results for the Primary Efficacy Endpoint MADRS

| Study Number | Treatment Group | Mean Baseline Score (SD) | LS Mean Change from Baseline (SE) | Placebo-subtracted Difference ^a (95% CI) |
|-------------------------|-------------------------------|--------------------------|-----------------------------------|---|
| Study 1 (fixed dose) | FETZIMA (ER 40 mg/day)* | 36.0 (4.1) | -14.8 (1.0) | -3.2 (-5.9, -0.5) |
| | FETZIMA (ER 80 mg/day)* | 36.1 (3.9) | -15.6 (1.0) | -4.0 (-6.7, -1.3) |
| | FETZIMA (ER 120 mg/day)* | 36.0 (3.9) | -16.5 (1.0) | -4.9 (-7.6, -2.1) |
| | Placebo | 35.6 (4.5) | -11.6 (1.0) | -- |
| Study 2 (fixed-dose) | FETZIMA (ER 40 mg/day)* | 30.8 (3.4) | -14.6 (0.8) | -3.3 (-5.5, -1.1) |
| | FETZIMA (ER 80 mg/day)* | 31.2 (3.5) | -14.4 (0.8) | -3.1 (-5.3, -1.0) |
| | Placebo | 31.0 (3.8) | -11.3 (0.8) | -- |
| Study 3 (flexible-dose) | FETZIMA (ER 40 - 120 mg/day)* | 35.0 (3.6) | -15.3 (0.8) | -3.1 (-5.3, -0.9) |
| | Placebo | 35.2 (3.8) | -12.2 (0.8) | -- |

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval unadjusted for multiplicity.

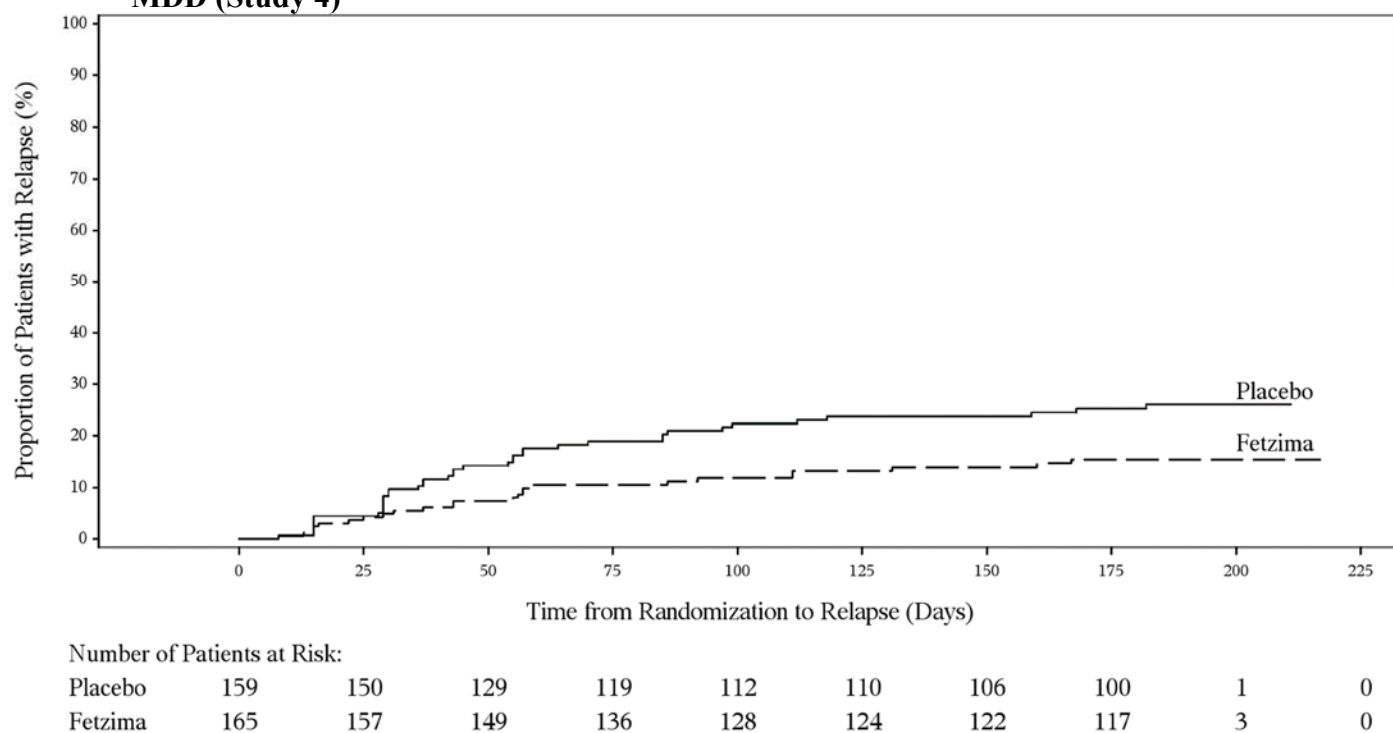
^a Difference (drug minus placebo) in least-squares mean change from baseline to endpoint (Week 8).

* Doses statistically significantly superior to placebo.

Post-hoc analyses of the relationships between treatment outcome and age, gender, and race did not suggest any differential responsiveness on the basis of these patient characteristics.

In a maintenance study (Study 4; NCT02288325), adult patients meeting DSM-5 criteria for MDD received flexibly dosed FETZIMA (40 mg, 80 mg, or 120 mg) once daily for 8 weeks. Responders in the initial 8-week treatment period were eligible to enter a 12-week, open-label, fixed-dose stabilization phase. At the end of stabilization, approximately half of the subjects were receiving 120 mg once daily. Three hundred twenty-four (324) patients who met the response criteria (MADRS total score ≤ 12) after 20 weeks of open-label treatment were randomized to the double-blind treatment phase with FETZIMA or placebo for 26 weeks. The primary efficacy endpoint was the time from randomization to first relapse during the double-blind phase. Relapse of depressive episode was defined as a MADRS total score ≥ 18 at two consecutive visits or insufficient therapeutic response as judged by the investigator. Patients on FETZIMA experienced a statistically significantly longer time to relapse than patients on placebo (Figure 3).

Figure 3. Kaplan-Meier Estimated Proportion of Patients with Relapse for Adults with MDD (Study 4)



Note: The estimated hazard ratio (95% CI) of FETZIMA relative to Placebo based on Cox proportional hazards model was 0.56 (95% CI: 0.33, 0.92).

16 HOW SUPPLIED/STORAGE AND HANDLING

FETZIMA extended-release capsules are supplied in the following configurations:

| Capsule Strength | Capsule Color/Shape | Capsule Markings | Package Configuration | NDC Code |
|------------------|---------------------------|--|--|--------------|
| 20 mg | yellow cap white body | black "FL" on cap black "20" on body | Bottle / 30 count | 0456-2220-30 |
| | | | Hospital Unit Dose (Blister) / 10 x 10 | 0456-2220-63 |
| 40 mg | yellow cap yellow body | black "FL" on cap black "40" on body | Bottle / 30 count | 0456-2240-30 |
| | | | Bottle / 90 count | 0456-2240-90 |
| | | | Hospital Unit Dose (Blister) / 10 x 10 | 0456-2240-63 |
| 80 mg | pink cap white body | black "FL" on cap black "80" on body | Bottle / 30 count | 0456-2280-30 |
| | | | Bottle / 90 count | 0456-2280-90 |
| | | | Hospital Unit Dose (Blister) / 10 x 10 | 0456-2280-63 |
| 120 mg | pink cap pink body | black "FL" on cap black "120" on body | Bottle / 30 count | 0456-2212-30 |
| | | | Bottle / 90 count | 0456-2212-90 |
| | | | Hospital Unit Dose (Blister) / 10 x 10 | 0456-2212-63 |

FETZIMA Titration Pack is supplied in the following configuration:

| Capsule Strength | Capsule Color/Shape | Capsule Markings | Package Configuration | NDC Code |
|------------------|---------------------------|---|---|--------------|
| 20 mg | yellow cap white body | black "FL" on cap black "20" on body | Titration Pack (Blister) containing two 20 mg capsules and twenty-six 40 mg capsules | 0456-2202-28 |
| 40 mg | yellow cap yellow body | black "FL" on cap black "40" on body | | |

Storage and Handling

All package configurations: Store at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Suicide Thoughts and Behaviors

Advise patients and caregivers to look for the emergence of suicidal thoughts and behaviors, especially early during treatment and when the dose is adjusted up or down [see Box Warning and Warnings and Precautions (5.1)].

Dosing and Administration

Advise patients that FETZIMA should be swallowed whole and should not be chewed, crushed or opened.

Advise patients that FETZIMA can be taken with or without food.

Instruct patients if they miss a dose, to take the missed dose as soon as they remember. If it is almost time for the next dose, instruct them to skip the missed dose and take their next dose at the regular time. Advise them not to take two doses of FETZIMA at the same time.

Concomitant Medication

Instruct patients not to take FETZIMA with an MAOI or within 14 days of stopping an MAOI and to allow 7 days after stopping FETZIMA before starting an MAOI [*see Contraindications (4)*].

Allergic Reactions

Advise patients to notify their healthcare provider if they develop an allergic reaction such as rash, hives, swelling, or difficulty breathing [*see Contraindications (4)*].

Serotonin Syndrome

Caution patients about the risk of serotonin syndrome, particularly with the concomitant use of FETZIMA with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, amphetamines, tryptophan, buspirone, and St. John's Wort supplements) [*see Warnings and Precautions (5.2) and Drug Interactions (7.1)*].

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)*].

Increased Risk of 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 [*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)*].

Sexual Dysfunction

Advise patients that use of Fetzima may cause symptoms of sexual dysfunction in both male and female patients. Inform patients that they should discuss any changes in sexual function and potential management strategies with their healthcare provider [*see Warnings and Precautions (5.12)*].

Alcohol

Advise patients to avoid consumption of alcohol while taking FETZIMA [*see Drug Interactions (7.1), Clinical Pharmacology (12.3)*].

Pregnancy

- Advise pregnant women to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with FETZIMA.
- Advise patients that FETZIMA use in late pregnancy may lead to an increased risk for postpartum hemorrhage and may increase the risk of neonatal complications requiring prolonged hospitalization, respiratory support, tube feeding.
- Advise women that there is a risk of relapse with discontinuation of antidepressants.
- Advise patient that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to FETZIMA during pregnancy [*see Use in Specific Populations (8.1)*]

Lactation

Advise breastfeeding women using FETZIMA to monitor infants for sedation, agitation, irritability, poor feeding and poor weight gain and to seek medical care if they notice these signs [*see Use in Specific Populations (8.2)*].

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, for oral use

What is the most important information I should know about FETZIMA?

FETZIMA may cause serious side effects, including:

- **Increased risk of suicidal thoughts or actions in some children, adolescents, and young adults.** FETZIMA and other antidepressant medicines may increase suicidal thoughts or actions in some children and young adults, **especially within the first few months of treatment or when the dose is changed. FETZIMA is not for use in children.**
 - **Depression or other serious mental illnesses are the most important causes of suicidal thoughts or actions. Some people may have a higher risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) depression, bipolar illness (also called manic-depressive illness) or have a history of suicidal thoughts or actions.

How can I watch for and try to prevent suicidal thoughts and actions?

- Pay close attention to any changes, especially sudden changes in mood, behavior, thoughts, or feelings, or if you develop suicidal thoughts or actions. 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 or get emergency medical help right away if you or your family member have any of the following symptoms, especially if they are new, worse, or worry you:

- attempts to commit suicide
- acting aggressive, being angry or violent
- new or worse depression
- panic attacks
- new or worse irritability
- an extreme increase in activity or talking (mania)
- acting on dangerous impulses
- thoughts about suicide or dying
- new or worsening anxiety
- feeling very agitated or restless
- trouble sleeping
- other unusual changes in behavior or mood

What is FETZIMA?

FETZIMA is a prescription medicine used to treat a certain type of depression called Major Depressive Disorder (MDD) in adults.

It is not known if FETZIMA is safe and effective for use in children.

It is not known if FETZIMA is safe and effective for the management of fibromyalgia. FETZIMA is not for use for the management of fibromyalgia.

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)
- have stopped taking an MAOI in the last 14 days
- are being treated with the antibiotic linezolid or intravenous methylene blue

Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid or intravenous methylene blue.

Do not start taking an MAOI for at least 7 days after you stop treatment with FETZIMA.

Before taking FETZIMA, tell your healthcare provider about all your medical conditions, including if you:

- have or have a family history of suicide, depression, bipolar disorder, mania or hypomania
- have high blood pressure
- have or had heart problems or stroke
- have or had bleeding problems
- have glaucoma (high pressure in the eye)
- have or had problems urinating (hesitation) or emptying your bladder (retention)
- have or had seizures (convulsions)
- have low sodium levels in your blood
- have or had kidney problems
- drink alcohol
- are pregnant or plan to become pregnant. FETZIMA may harm your unborn baby. Taking FETZIMA during your third trimester of pregnancy may cause an increased risk of bleeding after delivery and may cause harm to your baby. Talk to your healthcare provider about the risks to you and your baby if you take FETZIMA during pregnancy.
 - Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with FETZIMA.
 - There is a pregnancy registry for females who are exposed to FETZIMA during pregnancy. The purpose of the registry is to collect information about the health of females exposed to FETZIMA and their baby. If you become pregnant during treatment with FETZIMA, talk to your healthcare provider about registering with the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or visit online at <https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/>.
- are breastfeeding or plan to breastfeed. It is not known if FETZIMA passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with FETZIMA.
 - If you breastfeed during treatment with FETZIMA, call you healthcare provider right away if your baby develops sleepiness or fussiness, or is not feeding or gaining weight well.

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

FETZIMA and other medicines may affect each other causing possible serious side effects.

FETZIMA may affect the way other medicines work and other medicines may affect the way FETZIMA works.

Especially tell your healthcare provider if you take:

- MAOIs
- medicines used to treat migraine headache known as triptans
- tricyclic antidepressants
- fentanyl
- lithium
- tramadol
- tryptophan
- buspirone
- amphetamines
- St. John's Wort
- medicines that can affect blood clotting such as aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs) and warfarin
- diuretics
- medicines used to treat mood, anxiety, psychotic or thought disorders, including selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs)

Ask your healthcare provider if you are not sure if you are taking any of these medicines. Your healthcare provider can tell you if it is safe to take FETZIMA with your other medicines.

Do not start or stop any other medicines during treatment with FETZIMA without talking to your healthcare provider first. Stopping FETZIMA suddenly may cause you to have serious side effects. See, **“What are the possible side effects of FETZIMA?”**

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

How should I take FETZIMA?

- Take FETZIMA exactly as your healthcare provider tells you to take it. Do not change your dose or stop taking FETZIMA without first talking to your healthcare provider.
- Your healthcare provider may need to change the dose of FETZIMA until it is the right dose for you.
- Take FETZIMA 1 time each day at about the same time each day.
- Take FETZIMA with or without food.
- Swallow FETZIMA capsules whole. Do not open, chew, or crush the FETZIMA capsule.
- 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 2 doses of FETZIMA at the same time.
- If you take too much FETZIMA, call your healthcare provider or 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?

- Do not drive, operate heavy machinery, or do other dangerous activities until you know how FETZIMA affects you. FETZIMA can cause sleepiness or may affect your ability to make decisions, think clearly, or react quickly.
- Avoid drinking alcohol during treatment with FETZIMA.

What are the possible side effects of FETZIMA?

FETZIMA may cause serious side effects, including:

- See, **“What is the most important information I should know about FETZIMA?”**
- **Serotonin syndrome.** A potentially life-threatening problem called serotonin syndrome can happen when FETZIMA is taken with certain other medicines. See, **“Who should not take FETZIMA?”** Stop taking FETZIMA and call your healthcare provider or go to the nearest hospital emergency room right away if you have any of the following signs and symptoms of serotonin syndrome:
 - agitation
 - confusion
 - fast heart beat
 - dizziness
 - flushing
 - tremors, stiff muscles, or muscle twitching
 - seizures
 - seeing or hearing things that are not real (hallucinations)
 - coma
 - blood pressure changes
 - sweating
 - high body temperature (hyperthermia)
 - loss of coordination
 - nausea, vomiting, diarrhea
- **High blood pressure (hypertension).** Your healthcare provider should check your blood pressure before you start and during treatment with FETZIMA. If you have high blood pressure, it should be controlled before you start treatment with FETZIMA.
- **Increased heart rate.** Your healthcare provider should check your heart rate before you start and during treatment with FETZIMA. If you have heart problems or problems with an abnormal heartbeat, your problems should be treated before you start treatment with FETZIMA.
- **Increased risk of bleeding.** Taking FETZIMA with aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), warfarin or blood thinners may add to this risk. Tell your healthcare provider right away about any unusual bleeding or bruising.

- **Eye problems (angle-closure glaucoma).** Many antidepressant medicines, including FETZIMA, may cause a certain type of eye problem called angle-closure glaucoma. Call your healthcare provider if you have changes in your vision or eye pain.
- **Problems with urination.** FETZIMA may cause you to have problems with urination including decreased urine flow and being unable to pass any urine. Tell your healthcare provider if you develop any problems with urine flow during treatment with FETZIMA.
- **Manic episodes.** Manic episodes may happen in people with bipolar disorder who take FETZIMA. Symptoms may include:
 - greatly increased energy
 - racing thoughts
 - unusually grand ideas
 - talking more or faster than usual
 - severe trouble sleeping
 - reckless behavior
 - excessive happiness or irritability
- **Seizures (convulsions).**
- **Discontinuation syndrome.** Suddenly stopping FETZIMA may cause you to have serious side effects. Your healthcare provider may want to decrease your dose slowly. Symptoms may include:
 - changes in your mood
 - irritability and agitation
 - dizziness
 - electric shock sensation (paresthesia)
 - anxiety
 - confusion
 - headache
 - tiredness
 - problems sleeping
 - hypomania
 - ringing in your ears (tinnitus)
 - seizures
- **Low sodium levels in your blood (hyponatremia).** Low sodium levels in your blood may be serious and may cause death. Elderly people may be at greater risk for this. Signs and Symptoms of low sodium levels in your blood may include:
 - headache
 - memory changes
 - weakness and unsteadiness on your feet which can lead to falls
 - difficulty concentrating
 - confusion

In severe or more sudden cases, signs and symptoms include:

 - hallucinations (seeing or hearing things that are not real)
 - seizures
 - respiratory arrest
 - fainting
 - coma
 - death
- **Sexual problems (dysfunction).** Taking serotonin and norepinephrine reuptake inhibitors (SNRIs), including Fetzima, may cause sexual problems. Symptoms in males may include:
 - Delayed ejaculation or inability to have an ejaculation
 - Problems getting or keeping an erection
 - Decreased sex driveSymptoms in females may include:
 - Decreased sex drive
 - Delayed orgasm or inability to have an orgasm

Talk to your healthcare provider if you develop any changes in your sexual function or if you have any questions or concerns about sexual problems during treatment with FETZIMA. There may be treatments your healthcare provider can suggest.

The most common side effects of FETZIMA, include:

- nausea
- sweating
- erectile dysfunction
- constipation
- abnormal heartbeat
- vomiting

These are not all the possible side effects of FETZIMA.

Call your doctor 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 symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about FETZIMA that is written for healthcare professionals.

What are the ingredients in FETZIMA?

Active ingredient: levomilnacipran hydrochloride

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

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

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