MPR

PRESCRIBING ALERT®

Dear Healthcare Professional,

At *MPR* we strive to bring you important drug information in a concise and timely manner. In keeping with this goal, we are pleased to provide you with this PRESCRIBING ALERT containing detailed information on FETZIMA™ (levomilnacipran extended-release capsules), manufactured by Forest Pharmaceuticals, Inc.

FETZIMA is an FDA-approved serotonin and norepinephrine reuptake inhibitor (SNRI) therapy indicated for the treatment of major depressive disorder (MDD) in adults. FETZIMA is not approved for the management of fibromyalgia, and its efficacy and safety have not been established for that use.[1]

FETZIMA is available in 3 effective dosage strengths as 40 mg, 80 mg, and 120 mg capsules that provide dosing flexibility.[1]

Important Safety 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.

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.

FETZIMA is not approved for use in pediatric patients.

Contraindications

- FETZIMA is contraindicated in patients with a 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 due to 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.
  Starting FETZIMA in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated due to an increased risk of serotonin syndrome.
- Do not use FETZIMA in patients with uncontrolled narrow-angle glaucoma. In clinical studies, FETZIMA was associated with an increased risk of mydriasis.

Warnings and Precautions

- **All patients being treated with antidepressants should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the first few months of treatment and when increasing or decreasing the dose**. Consider changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or includes symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, mania, or suicidality that are severe, abrupt in onset, or were not part of the patient's presenting symptoms. **Families and caregivers of patients being treated with antidepressants should be alerted about the need to monitor patients daily**. 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.
- **Serotonin Syndrome:** The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs both when taken alone, but especially when co-administered with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue). Symptoms of serotonin syndrome may include mental status changes (eg, agitation, hallucinations, delirium, and coma), autonomic instability (eg, tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (eg, tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms. If symptoms of serotonin syndrome occur, discontinue FETZIMA immediately and initiate supportive treatment. If concomitant use of FETZIMA with other serotonergic drugs is clinically

(Important Safety Information continued on next page)

warranted, patients should be aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

- 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. Use with caution in patients with pre-existing hypertension, cardiovascular, or cerebrovascular conditions that might be compromised by increases in blood pressure. 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. For patients who experience a sustained increase in blood pressure, discontinuation or other appropriate medical intervention should be considered.
- SNRIs, including FETZIMA, have been associated with an increase in 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, discontinuation or other appropriate medical intervention should be considered.
- SSRIs and SNRIs, including FETZIMA, may increase the risk of bleeding events, some serious. Concomitant use of aspirin, NSAIDs, warfarin, and other anticoagulants may add to this risk.
- Mydriasis has been reported in association with SNRIs including FETZIMA; therefore, FETZIMA should be used with caution in patients with controlled narrow-angle glaucoma. Patients with raised intraocular pressure or those at risk of acute narrow-angle (angle-closure) glaucoma should be monitored. DO NOT use FETZIMA in patients with uncontrolled narrow-angle glaucoma.
- FETZIMA can affect urethral resistance. In clinical 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 when using FETZIMA in patients prone to obstructive urinary disorders.
- Symptoms of mania/hypomania were reported in 0.2% of FETZIMA-treated patients and 0.2% of placebo-treated patients in clinical studies. As with all antidepressants, FETZIMA should be used cautiously in patients with a history or family history of bipolar disorder, mania or hypomania. Prior to initiating treatment with FETZIMA, patients should be adequately screened to determine if they are at risk for bipolar disorder. FETZIMA is not approved for use in treating bipolar depression.
- FETZIMA should be prescribed with caution in patients with a seizure disorder.
- Discontinuation symptoms, some serious, have been reported with discontinuation of serotonergic antidepressants such as FETZIMA. Gradual dose reduction is recommended, instead of abrupt discontinuation, whenever possible. Monitor patients 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.
- 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. Although no cases of hyponatremia resulting from FETZIMA treatment were reported in the clinical studies, hyponatremia has occurred as a result of treatment with SSRIs and SNRIs. FETZIMA should be discontinued in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Adverse Reactions

The most commonly observed adverse reactions in MDD patients treated with FETZIMA 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.

Please see the full Prescribing Information.

More information regarding the use of FETZIMA is available in the current edition of *MPR*.

Sincerely,

Madonna Krawczyk, PharmD
Director of Clinical Communications
MPR Custom Programs

REFERENCE

1. Fetzima (levomilnacipran extended-release capsules) [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc.; 2013.

Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.

Licensed from Pierre Fabre Medicament.

FETZIMA™

levomilnacipran extended-release capsules

℞

Company: Forest Pharmaceuticals, Inc.
Pharmacologic Class: Serotonin and norepinephrine reuptake inhibitor (SNRI).
Active Ingredient: Levomilnacipran 20 mg, 40 mg, 80 mg, 120 mg; extended-release capsules.
Indication: Treatment of major depressive disorder (MDD) in adults. FETZIMA is not approved for the management of fibromyalgia and its efficacy and safety have not been established for that use.
Mechanism of Action: The exact mechanism of the antidepressant action 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).
Dosing: Initially 20 mg once daily for 2 days, and then increase to 40 mg once daily; may increase dose in 40 mg increments at intervals of ≥2 days; max 120 mg once daily.
Specific Populations: Pregnancy: Cat. C. Nursing mothers: Consider whether benefit outweighs risk. Pediatrics: The safety and effectiveness have not been established. Renal impairment: moderate (CrCl 30–59 mL/min): max 80 mg once daily; severe (CrCl 15–29 mL/min): max 40 mg once daily. ESRD: not recommended.
Contraindications: Hypersensitivity to levomilnacipran, milnacipran HCl, or any excipient in FETZIMA. MAOI use while using, or within 7 days of stopping, FETZIMA. FETZIMA use within 14 days of stopping an MAOI. Concomitant linezolid or IV methylene blue. Uncontrolled narrow-angle glaucoma, because of risk of mydriasis.
Warnings & Precautions: Monitor patients for clinical worsening and suicidal thinking or behavior. If concomitant use of FETZIMA with other serotonergic drugs is clinically warranted, caution patients of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases. If such symptoms occur, discontinue FETZIMA and initiate supportive treatment. Elevated blood pressure and heart rate may occur. Measure prior to initiating and periodically throughout treatment. Control pre-existing hypertension before initiating FETZIMA. 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. Mydriasis has occurred with FETZIMA. Use cautiously in patients with controlled narrow-angle glaucoma. Monitor patients with raised intraocular pressure or those at risk. If symptoms of urinary hesitation or retention occur, discontinue FETZIMA or consider other appropriate medical intervention. Screen patients for bipolar disorder, caution patients about risk of activation of mania/hypomania. Use with caution in patients with a seizure disorder. Taper dose when possible and monitor for discontinuation symptoms. Patients taking diuretics, who are volume-depleted, or elderly may be at a higher risk for hyponatremia. **(See Important Safety Information below and throughout.)**
Drug Interactions: See Contraindications. Allow at least 14 days after MAOI discontinuation before starting levomilnacipran; allow at least 7 days after discontinuing levomilnacipran before starting an MAOI. Increased risk of serotonin syndrome with other serotonergic drugs (eg, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, St. John's wort) or with drugs that impair serotonin metabolism (eg, MAOIs, linezolid, IV methylene blue). Increased risk of bleeding with concomitant NSAIDs, aspirin, anticoagulants; monitor. Concomitant strong CYP3A4 inhibitors (eg, ketoconazole, clarithromycin, ritonavir): adjust dose to max 80 mg once daily. Avoid alcohol. Caution with other CNS-active drugs, or drugs that can increase BP or HR.
Adverse Reactions: Most common (incidence ≥5% and at least twice the rate of placebo): nausea (17% vs 6%), constipation (9% vs 3%), hyperhidrosis (9% vs 2%), heart rate increased (6% vs 1%), erectile dysfunction (6% vs 1%), tachycardia (6% vs 2%), vomiting (5% vs 1%), and palpitations (5% vs 1%).
How Supplied: 20, 40, 80, and 120 mg capsules–30-count bottles; Titration Pack–1 (2 x 20 mg + 26 x 40 mg).

Important Safety Information

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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.

FETZIMA is not approved for use in pediatric patients.

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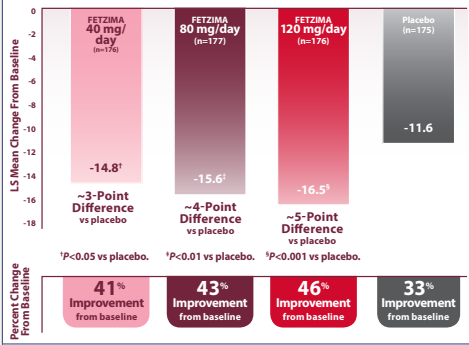
The efficacy of FETZIMA™ (levomilnacipran extended-release capsules) for the treatment of major depressive disorder (MDD) in adults (18–78 years of age; N=1709) was established in three 8-week randomized, double-blind, placebo-controlled studies (at doses 40–120 mg once daily)[1]

Significant improvement in depressive symptoms demonstrated across 3 dosage strengths: 40 mg, 80 mg, and 120 mg taken once daily[1]

In a fixed-dose study, FETZIMA demonstrated significant improvement in depressive symptoms across 3 dosage strengths

- Significant reductions in depressive symptoms vs placebo were achieved in MDD patients with a mean baseline Montgomery-Asberg Depression Rating Scale (MADRS) total score of 36[1,2]

PRIMARY EFFICACY ENDPOINT: MADRS MEAN TOTAL SCORE REDUCTION FROM BASELINE AT WEEK 8 (FIXED-DOSE STUDY*)[1,3]



- The primary efficacy endpoint was the change in MADRS total score from baseline to week 8 in the mITT population[3]
- The LS mean difference (95% CI) from placebo in change from baseline in MADRS total score was -3.2 (-5.9, -0.5) at 40 mg/day, -4.0 (-6.7, -1.3) at 80 mg/day, and -4.9 (-7.6, -2.1) at 120 mg/day[1,3]
- Mean baseline MADRS total score values: 36.0 (40 mg), 36.1 (80 mg), 36.0 (120 mg), 35.6 (placebo)[1]

CI = confidence interval; LS = least squares; MADRS = Montgomery-Asberg Depression Rating Scale; mITT = modified intention-to-treat; MMRM = mixed-effects model repeated measure.

*Randomized, double-blind, placebo-controlled, multicenter, 8-week study to determine the efficacy, safety, and tolerability of FETZIMA in adults aged 18 to 65 years who were diagnosed with MDD. MMRM analyses shown. FETZIMA treatment was initiated once daily at 20 mg on day 1, followed by 40 mg on day 3; 80 mg/day and 120 mg/day target doses were reached on day 5 and day 8, respectively. Patients continued on target doses until the end of week 8. FETZIMA was administered with or without food.[1,3]

For the secondary efficacy endpoint, FETZIMA demonstrated significant improvement in functional impairment over placebo as measured by the mean change in Sheehan Disability Scale (SDS) total score from baseline to Week 8*

- In the modified intention-to-treat (mITT) population, the least squares (LS) mean difference (95% confidence interval [CI]) from placebo in change from baseline in SDS total score was -1.4 (-3.4, 0.6) at 40 mg/day (n=151; *P*=not significant), -2.5 (-4.5, -0.5) at 80 mg/day (n=155; *P*<0.05 vs placebo), and -2.6 (-4.6, -0.5) at 120 mg/day (n=146; *P*<0.05 vs placebo)[2,3]
  - The difference was not statistically significant vs placebo at 40 mg/day and was statistically significant vs placebo at 80 mg and 120 mg/day[3]
- Mean baseline SDS total scores: 21.1 (40 mg), 21.4 (80 mg), 21.3 (120 mg), 21.5 (placebo)[3]

Important Safety Information *(continued)*

Contraindications

- FETZIMA is contraindicated in patients with a 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 due to 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.

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In an additional fixed-dose study, both doses (40 mg and 80 mg/day) achieved significant improvement in depressive symptoms and functional impairment vs placebo[1,4,‖]

- MADRS mean total score change from baseline at week 8: -14.6 at 40 mg/day (n=185; *P*<0.01); -14.4 at 80 mg/day (n=187; *P*<0.01); -11.3 for placebo (n=185)[1,4]
- SDS mean total score change from baseline at week 8: -7.3 at 40 mg/day (*P*<0.05); -8.2 at 80 mg/day (*P*<0.01); -5.4 for placebo[4]

‖Randomized, double-blind, placebo-controlled, multicenter, 8-week study to determine the efficacy, safety, and tolerability of FETZIMA in adults aged 18 to 75 years who were diagnosed with MDD. Patients were randomized to receive FETZIMA (n=372) or placebo (n=185). MMRM analyses shown.[1,4]

The primary efficacy endpoint was the change in MADRS total score from baseline to week 8 in the mITT population. The LS mean difference (95% CI) from placebo in change from baseline in MADRS total score was -3.3 (-5.5, -1.1) at 40 mg/day and -3.1 (-5.3, -1.0) at 80 mg/day. The secondary efficacy endpoint was the change in SDS total score from baseline to week 8 in the mITT population. The LS mean difference (95% CI) from placebo in change from baseline in SDS total score was -1.8 (-3.6, 0.0) at 40 mg/day and -2.7 (-4.5, -0.9) at 80 mg/day.[1,4]

FETZIMA treatment was initiated once daily at 20 mg on day 1, followed by 40 mg on day 3; 80 mg/day target dose was reached on day 6. Patients continued on target doses until the end of week 8. FETZIMA was administered with or without food.[1,4]

Important Safety Information *(continued)*

Contraindications

- Starting FETZIMA in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated due to an increased risk of serotonin syndrome.
- Do not use FETZIMA in patients with uncontrolled narrow-angle glaucoma. In clinical studies, FETZIMA was associated with an increased risk of mydriasis.

Warnings and Precautions

- **All patients being treated with antidepressants should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the first few months of treatment and when increasing or decreasing the dose.** Consider changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or includes symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, mania, or suicidality that are severe, abrupt in onset, or were not part of the patient's presenting symptoms. **Families and caregivers of patients being treated with antidepressants should be alerted about the need to monitor patients daily.** 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.
- **Serotonin Syndrome:** The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs both when taken alone, but especially when co-administered with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue). Symptoms of serotonin syndrome may include mental status changes (eg, agitation, hallucinations, delirium, and coma), autonomic instability (eg, tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (eg, tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms. If symptoms of serotonin syndrome occur, discontinue FETZIMA immediately and initiate supportive treatment. If concomitant use of FETZIMA with other serotonergic drugs is clinically warranted, patients should be aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.
- 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. Use with caution in patients with pre-existing hypertension, cardiovascular, or cerebrovascular conditions that might be compromised by increases in blood pressure. 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. For patients who experience a sustained increase in blood pressure, discontinuation or other appropriate medical intervention should be considered.

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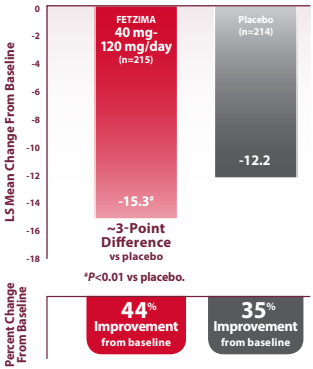
In a flexible-dose study, FETZIMA demonstrated significant improvement in depressive symptoms across the therapeutic range

- Significant reductions in depressive symptoms vs placebo were achieved in MDD patients with a mean baseline MADRS total score of 35[1,5]

PRIMARY EFFICACY ENDPOINT: MADRS MEAN TOTAL SCORE REDUCTION FROM BASELINE AT WEEK 8 (FLEXIBLE-DOSE STUDY¶)[1,5]



- The primary efficacy endpoint was the change in MADRS total score from baseline to week 8 in the mITT population[1,5]
- The LS mean difference (95% CI) from placebo in change from baseline in MADRS total score was -3.1 (-5.3, -0.9)[1,5]
- Mean baseline MADRS total score values: 35.0 for FETZIMA and 35.2 for placebo[1]
- 78% of patients were on either 80 mg or 120 mg of FETZIMA at the end of the study[1]

CI = confidence interval; LS = least squares; MADRS = Montgomery-Asberg Depression Rating Scale; mITT = modified intention-to-treat; MMRM = mixed-effects model repeated measure.

¶Randomized, double-blind, placebo-controlled, multicenter, 8-week study to determine the efficacy, safety, and tolerability of FETZIMA in adults aged 18 to 80 years who were diagnosed with MDD. MMRM analyses shown. FETZIMA treatment was initiated once daily at 20 mg on day 1, followed by 40 mg on day 3. Dose increase to 80 mg/day permitted at end of week 1 or 2; increase from 40 mg to 80 mg/day or 80 mg to 120 mg/day permitted at end of week 4 based on patient response and tolerability. Patients continued on target doses until the end of week 8. FETZIMA was administered with or without food.[1,5]

The secondary efficacy endpoint was the change in SDS total score from baseline to week 8 in the mITT population¶

- The LS mean difference (95% CI) from placebo in change from baseline in SDS total score was -2.6 (-4.2, -1.1) (P<0.01 vs placebo)[5]
- Mean baseline SDS total scores: 20.1 for FETZIMA and 19.7 for placebo[5]

Important Safety Information *(continued)*

Warnings and Precautions

- SNRIs, including FETZIMA, have been associated with an increase in 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, discontinuation or other appropriate medical intervention should be considered.
- SSRIs and SNRIs, including FETZIMA, may increase the risk of bleeding events, some serious. Concomitant use of aspirin, NSAIDs, warfarin, and other anticoagulants may add to this risk.
- Mydriasis has been reported in association with SNRIs including FETZIMA; therefore, FETZIMA should be used with caution in patients with controlled narrow-angle glaucoma. Patients with raised intraocular pressure or those at risk of acute narrow-angle (angle-closure) glaucoma should be monitored. DO NOT use FETZIMA in patients with uncontrolled narrow-angle glaucoma.
- FETZIMA can affect urethral resistance. In clinical 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 when using FETZIMA in patients prone to obstructive urinary disorders.

Please see additional Important Safety Information throughout, including Boxed Warning, and full Prescribing Information.

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The safety of FETZIMA was evaluated in 2673 patients (18–78 years of age) diagnosed with MDD who participated in clinical studies

ADVERSE EVENTS OCCURRING IN ≥2% OF FETZIMA-TREATED PATIENTS AND AT LEAST TWICE THE RATE OF PLACEBO-TREATED PATIENTS[1]

System Organ Class Preferred Term	Placebo (n=1040) %	FETZIMA 40 mg - 120 mg/day (n=1583) %
Gastrointestinal disorders		
Nausea	6	17
Constipation	3	9
Vomiting	1	5
Cardiac disorders		
Tachycardia	2	6
Palpitations	1	5
Reproductive system and breast disorders		
Erectile dysfunction	1	6
Testicular pain	<1	4
Ejaculation disorder	<1	5
Investigations		
Heart rate increased	1	6
Blood pressure increased	1	3
Renal and urinary disorders		
Urinary hesitation	0	4
Skin and subcutaneous tissue disorders		
Hyperhidrosis	2	9
Rash	0	2
Vascular disorders		
Hot flush	1	3
Hypotension	1	3
Hypertension	1	3
Metabolism and nutrition disorders		
Decreased appetite	1	3

- Fewer than 2% of FETZIMA-treated female MDD patients in placebo-controlled clinical studies reported adverse events related to sexual function[1]

The effect of FETZIMA on body weight[6]

- Pooled results from short-term studies demonstrated a mean change in the body weight of -0.59 kg for FETZIMA (n=1572) and +0.02 kg for placebo (n=1032)[2]
- Percentage of patients with clinically significant weight change (≥7%) in short-term studies[2,**]
  - — Increase: 0.6% FETZIMA, 0.9% placebo
  - — Decrease: 1.6% FETZIMA, 1.0% placebo
- In a 1-year, open-label, long-term safety study, the mean weight change from baseline was -0.55 kg[6]

**Pooled results from short-term, randomized, double-blind, placebo-controlled, multicenter studies in adult patients with MDD aged 18 to 78 years.[1,2]

Please see additional Important Safety Information throughout, including Boxed Warning, and full Prescribing Information.

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The only dose-related AEs (>2%) were urinary hesitation and erectile dysfunction in the fixed-dose studies[1]

- Dose-related adverse events in pooled data from short-term, placebo-controlled, fixed-dose studies were urinary hesitation (FETZIMA 40 mg/day [n=366]: 4%; 80 mg/day [n=367]: 5%; 120 mg/day [n=180]: 6%; placebo [n=362]: 0%) and erectile dysfunction (FETZIMA 40 mg/day [n=366]: 6%; 80 mg/day [n=367]: 8%; 120 mg/day [n=180]: 10%; placebo [n=362]: 2%)[1]

Discontinuation rates due to adverse reactions

- 9% of the 1583 patients who received FETZIMA (40 mg–120 mg) discontinued treatment due to an adverse reaction, compared with 3% of 1040 patients who received placebo[1]
- 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%)[1]
- Discontinuation due to urinary hesitation was 0.4% for FETZIMA and 0% for placebo[2]
- Discontinuation due to erectile dysfunction was 0.7% for FETZIMA and 0% for placebo[2]

Important Safety Information *(continued)*

Warnings and Precautions

- Symptoms of mania/hypomania were reported in 0.2% of FETZIMA-treated patients and 0.2% of placebo-treated patients in clinical studies. As with all antidepressants, FETZIMA should be used cautiously in patients with a history or family history of bipolar disorder, mania or hypomania. Prior to initiating treatment with FETZIMA, patients should be adequately screened to determine if they are at risk for bipolar disorder. FETZIMA is not approved for use in treating bipolar depression.
- FETZIMA should be prescribed with caution in patients with a seizure disorder.
- Discontinuation symptoms, some serious, have been reported with discontinuation of serotonergic antidepressants such as FETZIMA. Gradual dose reduction is recommended, instead of abrupt discontinuation, whenever possible. Monitor patients 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.
- 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. Although no cases of hyponatremia resulting from FETZIMA treatment were reported in the clinical studies, hyponatremia has occurred as a result of treatment with SSRIs and SNRIs. FETZIMA should be discontinued in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Adverse Reactions

The most commonly observed adverse reactions in MDD patients treated with FETZIMA 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.

Please see additional Important Safety Information throughout, including Boxed Warning, and full Prescribing Information.

REFERENCES

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