FETZIMA™ (levomilnacipran extended-release capsules) Fact Sheet

About FETZIMA

- FETZIMA (levomilnacipran), a once-daily, serotonin and norepinephrine reuptake inhibitor (SNRI), was approved by the U.S. Food and Drug Administration (FDA) for the treatment of Major Depressive Disorder (MDD) in adults in July 2013.

- While the exact mechanism is unknown, it 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.

- Forest Laboratories, Inc. expects FETZIMA to be available to wholesalers in the 4th calendar quarter 2013.

Pivotal Trial Clinical Data

- In the placebo-controlled, pivotal Phase III studies of adult patients with MDD, statistically significant and clinically meaningful improvement in depressive symptoms was demonstrated across three FETZIMA dosage strengths of 40, 80, and 120 mg once daily compared with placebo as measured by the Montgomery Åsberg Depression Rating Scale (MADRS) total score (primary endpoint). FETZIMA also demonstrated superiority over placebo as measured by improvement in the Sheehan Disability Scale (SDS) functional impairment total score (secondary endpoint).

- The efficacy of FETZIMA was demonstrated in three positive Phase III studies comprising two double-blind, fixed-dose studies and one flexible-dose study that compared FETZIMA with placebo in adults with MDD. A total of more than 1,600 adult patients received a once-daily dose of either FETZIMA (40, 80, 120 mg) or placebo in the three studies.

- The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) in the placebo-controlled trials were nausea, constipation, hyperhidrosis, heart rate increased, erectile dysfunction, tachycardia, vomiting and palpitations. Rates of adverse events were generally consistent across doses (40-120 mg); the only dose-related adverse events (greater than 2% overall incidence) were urinary hesitation and erectile dysfunction.

- In each of these studies, statistically significant improvement was seen in the FETZIMA group compared with placebo in the primary and secondary endpoints [mean change from baseline to endpoint in the Montgomery Åsberg Depression Rating Scale (MADRS) total score and Sheehan Disability Scale (SDS) total score, respectively] using the mixed-effects model for repeated measures (MMRM) and last-observation-carried-forward (LOCF) analyses.

Primary Endpoint MADRS (Reduction in depressive symptoms)

- In all three studies, FETZIMA demonstrated superiority over placebo in the improvement of depressive symptoms as measured by the change from baseline to week 8 in the MADRS total score. MADRS is a widely used, clinician-rated scale to assess the severity of 10 depressive symptoms. A total MADRS score of 35 or greater is suggestive of severe depression, a score of 18-34 is suggestive of moderate depression, and a score of 9-17 is suggestive of mild depression. The primary efficacy endpoint in the pivotal trials was change from baseline to week 8 in the total MADRS score. A 2-point difference between drug effect and placebo is generally considered to represent a clinically meaningful improvement in depressive symptoms.

    - For study 1, the mean baseline MADRS total score was 36 for all treatment groups. The LS mean difference from placebo in change from baseline was statistically significant at all three FETZIMA doses (-3.2 at 40 mg/day, -4.0 at 80 mg/day, and -4.9 at 120 mg/day).

For study 2, the mean baseline MADRS total score was 31 for all treatment groups. The LS mean difference from placebo in change from baseline was statistically significant at both FETZIMA doses studied (-3.3 at 40 mg/day, -3.1 at 80 mg/day). For study 3, the mean baseline MADRS total score was 35 for all treatment groups.The LS mean difference from placebo in change from baseline was statistically significant for the FETZIMA dosing range studied (-3.1 at 40-120 mg/day).

Secondary Endpoint Sheehan Disability Scale (Improvement in SDS functional impairment)

- FETZIMA also demonstrated superiority over placebo as measured by improvement in the Sheehan Disability Scale (SDS) functional impairment total score. SDS is a validated scale that measures the extent that emotional symptoms disrupt patient functioning in 3 life domains: work/school, social life, and family life with each item scored from 0 (unimpaired) to 10 (highly impaired).

FETZIMA Dosage and Administration

- FETZIMA can be taken with or without food.
- The recommended dose range for FETZIMA is 40-120 mg once daily.
- 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 daily.

Manufacturing and Marketing

- FETZIMA was discovered by Pierre Fabre and is licensed to Forest Laboratories, Inc. in the US and Canada. Pierre-Fabre will also be the active pharmaceutical ingredient (API) supplier.

More Information on FETZIMA

- Visit www.FETZIMA.com

Please see Important Safety Information, including Boxed Warning, below.

FETZIMA Indication and Usage

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

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

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.

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, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (eg, tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms. If symptoms of serotonin syndrome occur, discontinue FETZIMA 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. 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, warfarin, NSAIDs 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 should be monitored. DO NOT use FETZIMA in patients with uncontrolled narrow-angle glaucoma.
- SNRIs, including FETZIMA, can affect urethral resistance. 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 attached full Prescribing Information.

For more information on FETZIMA, please visit FETZIMA.com or call Forest Pharmaceuticals at 1-800-678-1605.

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