Forest Laboratories, Inc.

Fact Sheet

Committed to Advancing Mental Health

For more than 15 years, Forest Laboratories has been committed to the well-being of patients living with depression. As part of our growing mental health portfolio, Forest's franchise now includes two products for the treatment of Major Depressive Disorder (MDD) in adults – VIIBRYD® (vilazodone HCl) and FETZIMA™ (levomilnacipran extended-release capsules). MDD is a serious medical condition often requiring treatment, and people with MDD may struggle to find a treatment that works for them. Together, these products reflect Forest's research-driven approach toward identifying and developing a range of treatment options for the almost 16 million adults in the United States who experience MDD each year.

About VIIBRYD

VIIBRYD is the first and only FDA-approved selective serotonin reuptake inhibitor (SSRI) and 5-HT_{1A} receptor partial agonist for the treatment of adults with MDD. The mechanism of the antidepressant effect of vilazodone is not fully understood, but is thought to be related to its enhancement of serotonergic activity in the central nervous system (CNS) through selective inhibition of serotonin reuptake. Vilazodone is also a partial agonist at 5-HT_{1A} receptors; however, the net result of this action on serotonergic transmission and its role in the antidepressant effect of vilazodone are unknown. VIIBRYD was approved in 2011 and is available in pharmacies across the U.S.

About FETZIMA

FETZIMA is a once-daily serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for the treatment of MDD in adults. While the exact mechanism of levomilnacipran is unknown, it is thought to be related to the potentiation of serotonin and norepinephrine in the CNS, through inhibition of reuptake at serotonin and norepinephrine transporters. Non-clinical studies have shown that FETZIMA is a potent and selective serotonin and norepinephrine reuptake inhibitor.

FETZIMA was approved by the U.S. FDA in July 2013 and will be available in pharmacies in the 4th quarter of 2013.

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.

FETZIMA 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.

Please also see additional Important Safety Information for FETZIMA and VIIBRYD on the following pages.

FETZIMA 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.
- 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.

Please also see additional Important Safety Information for FETZIMA and VIIBRYD on the following pages.

FETZIMA Important Safety Information (continued)

- 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.

VIIBRYD Important Safety Information

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of VIIBRYD or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. VIIBRYD is not approved for use in pediatric patients.

Please also see additional Important Safety Information for VIIBRYD on the following pages.

VIIBRYD Important Safety Information (continued)

Contraindications

- **Serotonin Syndrome and MAOIs:** Do not use MAOIs intended to treat psychiatric disorders with VIIBRYD or within 14 days of stopping treatment with VIIBRYD. Do not use VIIBRYD within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start VIIBRYD in a patient who is being treated with linezolid or intravenous methylene blue.

Warnings and Precautions

- **All patients 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 changing 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 VIIBRYD should be written for the smallest quantity of tablets 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, including VIIBRYD, 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 VIIBRYD and initiate supportive treatment. If concomitant use of VIIBRYD 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. Patients should be monitored for the emergence of serotonin syndrome.
- Like other antidepressants, VIIBRYD should be prescribed with caution in patients with a seizure disorder.
- The use of drugs that interfere with serotonin reuptake, including VIIBRYD, may increase the risk of bleeding events. Patients should be cautioned about the risk of bleeding associated with the concomitant use of VIIBRYD and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation or bleeding.
- Symptoms of mania/hypomania were noted in 0.1% of patients treated with VIIBRYD in clinical studies. As with all antidepressants, VIIBRYD should be used cautiously in patients with a history or family history of bipolar disorder, mania, or hypomania.
- Prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder. VIIBRYD is not approved for use in treating bipolar depression.

Please also see additional Important Safety Information for VIIBRYD on the following page.

VIIBRYD Important Safety Information (continued)

- Discontinuation symptoms have been reported with discontinuation of serotonergic drugs such as VIIBRYD. Gradual dose reduction is recommended, instead of abrupt discontinuation, whenever possible. Monitor patients when discontinuing VIIBRYD. 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 VIIBRYD. Although no cases of hyponatremia resulting from VIIBRYD treatment were reported in the clinical studies, hyponatremia has occurred as a result of treatment with SSRIs and SNRIs. Discontinuation of VIIBRYD 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 VIIBRYD in placebo-controlled studies (incidence ≥5% and at least twice the rate of placebo) were: diarrhea (28% vs 9%), nausea (23% vs 5%), insomnia (6% vs 2%), and vomiting (5% vs 1%).

Please see full Prescribing Information for VIIBRYD at www.VIIBRYD.com.

Please also see additional Important Safety Information, including the Boxed Warning, on the previous pages.

Forest Pharmaceuticals, Inc.
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