Drug Monograph

Drug/Drug Class:	**Fetzima™ (levomilnacipran hydrochloride) capsule, extended release / Serotonin and norepinephrine reuptake inhibitor**
Prepared for:	MO HealthNet
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☒ New Criteria ☐ Revision of Existing Criteria

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Each 20 mg, 40 mg, 80 mg and 12 mg extended release capsule of Fetzima™ contains 20 mg, 40 mg, 80 mg or 120 mg respectively of levomilnacipran hydrochloride. Forest Pharmaceuticals, Inc., St. Louis, Missouri 63045
Summary of Findings:	Fetzima, a potent and selective SNRI, is indicated for the treatment of major depressive disorder (MDD) in adults. Fetzima is not approved for the treatment of fibromyalgia as efficacy has not yet been studied.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Fiscal Edit ☒ Clinical Edit
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☒ Appropriate Indications ☐ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction[1,3]

Major depressive disorder is a debilitating disease that affects 16 million adults in the United States every year, which is an estimated 7.3% of the population age 18 and older in a given year.

Dosage Form(s) [1]

Fetzima 20 mg, 50 mg, 80 mg and 120 mg is available as extended release capsules containing 20 mg, 40 mg , 80 mg, or 120 mg Levomilnacipran respectively in 30 count bottles. It is also supplied as a titration pack containing two 20mg capsules and twenty-six 40mg capsules.

Manufacturer [1]

Forest Pharmaceuticals, Inc., St. Louis, Missouri 63045

Indication(s) [1]

Fetzima is indicated for the treatment of major depressive disorder in adults.

Clinical Efficacy [1-3] (mechanism of action/pharmacology, comparative efficacy)

Fetzima is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI) but its exact mechanism of antidepressant action is not fully known. Fetzima binds with high affinity to serotonin (5-HT) and norepinephrine (NE) transporters and potently inhibits the reuptake of 5-HT and NE. Its action is related to potentiation of the levels of serotonin and norepinephrine in the central nervous system.

Pharmacokinetics

	FETZIMA
Protein Binding	22%
Volume of Distribution	387 to 473 L
Metabolism	Desethylation to desethyl levomilnacipran; hydroxylation to p-hydroxy-levomilnacipran; both are inactive and form glucuronide conjugates.
Excretion	Renal (unchanged 58%; N-desethyl metabolite 18%)
Half-life	12 hours

The approval of Fetzima was based on three, 8-week, randomized, double-blind, placebo-controlled studies in adults with MDD as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR); 2 studies were fixed-dose (40 mg/day, 80 mg/day, or 120 mg/day) and one was a flexible-dose (40 to 120 mg/day) study. In all 3 studies, Fetzima treatment was superior to placebo in improvement of depressive symptoms as assessed by the Montgomery-Asberg

Depression Rating Scale (MADRS) and improvement in the Sheehan Disability Scale (SDS) functional impairment total scores.

MAJOR DEPRESSIVE DISORDER

STUDY DESIGN	Multicenter, randomized, double-blind, placebo-controlled, fixed-dose study
INCLUSION CRITERIA	Adults aged 18 to 65 years with MDD as defined by the DSM-IV-TR and confirmed by the Mini-International Neuropsychiatric Interview were included if they were experiencing a current ongoing depressive episode of at least 8 weeks duration, a baseline score of 30 or higher on the clinician-rated MADRS and of 26 or higher on the self-rated MADRS, a body mass index of 18 to 40, and were not pregnant.
EXCLUSION CRITERIA	Patients with clinically significant medical conditions (eg, CNS or cardiovascular disorders), abnormalities on physical examination, laboratory tests, or ECG; with DSM-IV-TR primary Axis I diagnoses different from MDD, a lifetime history of mania/hypomania, other significant psychiatric disorders, or substance abuse/dependence within 6 months; or at suicide risk (ie, suicide attempt within the previous year, score of 5 or higher on MADRS item 10 assessing suicidal thoughts, or significant risk based on investigator-assessed Columbia-Suicide Severity Rating Scale) were among those excluded.
TREATMENT REGIMEN	Following a 1-week, single-blind, placebo run-in period, patients (n=724) were randomized to receive extended-release Fetzima at a dose of 40 mg (n=181), 80 mg (n=181), 120 mg (n=183) mg, or placebo (n=179) orally once daily for 8 weeks followed by a 2-week, double-blind taper. The study drug was initiated at 20 mg/day, with dose increases to 40 mg/day on day 2 and to 80 mg/day and 120 mg/day on days 5 and 8, respectively. The efficacy endpoints of improvement in the MADRS baseline total score (primary) and the SDS functional impairment total score (secondary) were assessed in the modified intent-to-treat population (those receiving at least 1 study dose and with at least 1 post-baseline assessment). At baseline, the mean MADRS total score was 36, the SDS score ranged from 21.1 to 21.5, the mean duration of MDD was approximately 11 years, 76% of patients had a history of recurrent depression, and 50% had received antidepressant therapy within the previous 5 years.
RESULTS	At 8 weeks, the least squares mean (LSM) difference for improvement in baseline MADRS total score in all Fetzima groups was significantly superior to placebo: difference from placebo, -3.23 (p=0.0186), -3.99 (p=0.0038), and -4.86 (p=0.0005) for the 40 mg/day (n=176), 80 mg/day (n=177), and 120 mg/day (n=176) dose groups, respectively. For the 40 mg/day and 80 mg/day dose groups, a significant difference in the MADRS total score

	compared with placebo was evident by week 4. Among secondary endpoints, the LSM difference for change from baseline SDS score was significantly better than placebo only in the 80 mg/day and 120 mg/day dose groups (-2.51 and -2.57, respectively; $p < 0.05$ for both). For both the 80 mg/day and 120 mg/day dose groups, the LSM difference from placebo was also significant ($p < 0.05$ for all) for change in baseline Hamilton Depression Rating Scale (-2.09 and -2.34, respectively), baseline Clinical Global Impressions (CGI)-Severity of Illness (-0.43 and -0.35, respectively), and baseline CGI-Improvement scores (-0.34 and -0.32, respectively).
SAFETY	The most common treatment-emergent adverse events were mild to moderate in severity and included headache (Fetzima, 15% to 16.3%; placebo, 11.4%), nausea (Fetzima, 10.7% to 21.8%; placebo, 2.3%), constipation (Fetzima, 10.1% to 12.8%; placebo, 4%), dry mouth (Fetzima, 6.7% to 15%; placebo, 9.7%), heart rate increased (Fetzima, 6.1% to 10.1%; placebo, 1.7%), and hyperhidrosis (Fetzima, 5.1% to 13.4%; placebo, 2.3%).

Contraindications [(1)]

- Hypersensitivity to levomilnacipran, milnacipran hydrochloride, or to any excipient of the product.
- Concomitant use with an MAOI, including use within 14 days of discontinuing an MAOI used to treat psychiatric disorders or MAOI use within 7 days after levomilnacipran discontinuation; includes linezolid or IV methylene blue.
- Narrow-angle glaucoma, uncontrolled.

Warnings and Precautions [(1)]

- Suicidal ideation and behavior, worsening depression, or unusual changes in behavior may occur; increased risk in children, adolescents, and young adults (ages 18 to 24 years); monitor all patients closely, particularly during the first few months of therapy or when dose changes occur; discontinuation (tapered as rapidly as feasible) may be required.
- Serotonin syndrome, potentially life-threatening, has been reported with SNRIs and selective serotonin reuptake inhibitors (SSRIs); risk is higher with concomitant use of other serotonergic drugs (eg, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, St. John's Wort) and drugs that impair serotonin metabolism (eg, MAOIs, including linezolid and IV methylene blue); monitoring recommended; discontinue immediately if syndrome occurs.
- Blood pressure (BP) increases may occur; control preexisting hypertension prior to starting therapy; monitoring recommended and discontinuation may be necessary for sustained BP increases.
- Cardiovascular or cerebrovascular conditions, preexisting; potential for BP increases; monitoring recommended and discontinuation may be necessary for sustained BP increases.
- Heart rate increases may occur; treat preexisting tachyarrhythmias and other cardiac disease prior to starting therapy; discontinuation may be necessary for sustained heart rate elevation.

- Bleeding events (eg, life-threatening hemorrhages, gastrointestinal bleeding, ecchymosis, hematoma, epistaxis, petechiae) may occur; increased risk with concomitant use of drugs affecting coagulation (eg, NSAIDs, aspirin, and warfarin).
- Narrow-angle glaucoma, controlled; mydriasis has been reported; monitor patients with raised intraocular pressure and those at risk for acute narrow-angle glaucoma.
- Obstructive urinary disorders; urethral resistance may be affected, causing urinary hesitation, retention, or dysuria; may necessitate discontinuation of therapy.
- Mania, hypomania or bipolar disorder, history or family history; risk of activation.
- Seizures may occur; caution advised in patients with a seizure disorder.
- Abrupt withdrawal; potential for withdrawal symptoms; monitoring recommended; reduce dose gradually if possible.
- Concomitant use of alcohol not recommended as this may accelerate drug release.
- Hyponatremia and/or syndrome of inappropriate antidiuretic hormone secretion has been reported with SNRIs and SSRIs; increased risk in elderly, volume-depleted patients, and those on concomitant diuretic therapy; discontinuation recommended if symptomatic hyponatremia occurs.
- Renal impairment; dosage reduction recommended for moderate (CrCl, 30 to 59 mL/min) or severe impairment (CrCl, 5 to 29 mL/min); use not recommended in ESRD patients.

Adverse Effects [(1)]

Most common, >= 4%	Fetzima	Placebo
	(n=1583)	(n=1040)
Nausea	17%	6%
Constipation	9%	3%
Hyperhidrosis	9%	2%
Tachycardia	6%	2%
Heart rate increased	6%	1%
Erectile dysfunction	6%	1%
Palpitations	5%	1%
Vomiting	5%	1%
Ejaculation disorder	5%	< 1%
Urinary hesitation	4%	0%

Drug Interactions [(1)]

- Alcohol
- Drugs interfering with homeostasis: NSAIDs, aspirin, warfarin
- MAOIs
- Serotonergic drugs: triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, St. John's Wort
- Strong CYP3A4 inhibitors: ketoconazole

Dosage and Administration [(1)]

The recommended initial adult dose is 20 mg orally once daily for 2 days, then 40 mg once daily, at the same time each day. Dosage may be increased in 40-mg increments at intervals of 2 or more

days up to a maximum of 120 mg once daily. As efficacy has only been established for 8 weeks, reassess periodically for maintenance therapy at the appropriate dose. In renal Impairment, the recommendation is 80 mg once daily for moderate and 40 mg once daily for severe impairment.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST/ MONTH
Levomilnacipran hydrochloride	Fetzima	Forest	20 mg extended-release capsules	1 capsule daily	$202.50
			40 mg extended-release capsules	1 capsule daily	$202.50
			80 mg extended-release capsules	1 capsule daily	$202.50
			120 mg extended-release capsules	1 capsule daily	$202.50

*WholesaleAcquisitionCost

Conclusion

Fetzima, a potent and selective SNRI, is indicated for the treatment of MDD in adults. The three 8-week, randomized, double-blind, placebo-controlled studies in adults with MDD, Fetzima demonstrated efficacy in improving depressive symptoms compared to placebo and improvement in the Sheehan Disability Scale (SDS) functional impairment total scores. This led to its approval for treatment of MDD. But the efficacy and safety of Fetzima for the management of fibromyalgia have not been established. Close monitoring is recommended in children, adolescents, and young adults due to increased risk of suicidal ideation and behavior, worsening depression, or unusual changes in behavior that may occur with Fetzima.

Recommendation

The Division recommends adding this drug to the current SNRI and psychotropic polypharmacy clinical edits.

References

1. Product Information: Fetzima™, levomilnacipran oral extended-release capsules. Forest Pharmaceuticals, Inc, St. Louis, MO, 07/2013.

2. Asnis GM, Bose, A, Gommoll CP et al: Efficacy and safety of levomilnacipran sustained-release 40 mg, 80 mg, and 120 mg in major depressive disorder: A phase 3, randomized, double-blind, placebo-controlled study. J Clin Psychiatry 2013; 74(30):242-248.

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