PDL NEW DRUG REVIEW

Proprietary Name: Fetzima®
Common Name: levomilnacipran extended-release
PDL Category: Antidepressants

Comparable Products	Preferred Drug List Status
Cymbalta	Preferred
Venlafaxine ER	Preferred

Summary

Indications and Usage: For the treatment of major depressive disorder (MDD) in adults. The efficacy of use was established in three 8-week trials. Fetzima® is not approved for the management of fibromyalgia, as the safety and efficacy for use as treatment have not been established. This is a pregnancy category C medication. The safety and efficacy of use in children have not been established. In addition, Fetzima® has a box warning indicating that there may be an increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants. Furthermore, the box warning indicates it's not approved for use in the pediatric population.

Drug Interactions: The concomitant use or use within 1-2 weeks after discontinuation with an MAOI is contraindicated. If the concomitant use with other serotonergic drugs, including triptans, TCAs, fentanyl, lithium, tramadol, buspirone, tryptophan, and St. John's Wort, is clinically warranted, it should be done with caution and the patient should be aware of the potential for increased risk of serotonin syndrome. Increased bleeding has been reported in those taking an SSRI or SNRI concomitantly with warfarin; thus, carefully monitor patients receiving warfarin if Fetzima® is initiated or discontinued. Use caution if administering Fetzima® concomitantly with other CNS-acting drugs, including those with a similar mechanism of action. The concomitant use of Fetzima® with alcohol is not recommended. Last, the dose of Fetzima® should not exceed 80mg once daily when used concomitantly with a strong CYP3A4 inhibitor (i.e. ketoconazole, clarithromycin, ritonavir).

Dosage Forms: Capsules, extended-release: 20mg, 40mg, 80mg, and 120mg

Recommended Dosage: Take 40mg to 120mg once daily, with or without food after initial dose titration starting at 20mg daily. Capsules should not be opened, chewed, or crushed.

Dose adjustments are not needed in those with mild renal impairment; however, the maintenance dose should not exceed 80mg once daily for those with moderate renal impairment or should not exceed 40mg once daily for those with severe renal impairment. Use in those with end stage renal disease is not recommended. Dose adjustment is not required in those with hepatic impairment.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Fetzima®) minus reported % incidence for placebo. Please note that the adverse events listed with an incidence of*

0% below means that the adverse reaction was reported but the incidence was less with Fetzima® than with placebo. The most commonly reported adverse events with Fetzima® include nausea (11%), constipation (6%), vomiting (4%), tachycardia (4%), palpitations (4%), erectile dysfunction (5%), testicular pain (>3%), ejaculation disorder (>4%), heart rate increased (5%), blood pressure increased (2%), urinary hesitation (4%), hyperhidrosis (7%), rash (2%), hot flush (2%), hypotension (2%), hypertension (2%), and decreased appetite (2%).

In short-term trials, there was an associated mean increase in heart rate of 7.4 beats per minute (bpm) with Fetzima® as compared with a mean decrease of 0.3 bpm with placebo. If a sustained increase in heart rate occurs during Fetzima use, discontinue treatment or consider other appropriate medical intervention.

Increases in blood pressure have been associated with SNRIs, including Fetzima®. Pre-existing conditions of hypertension should be controlled prior to starting treatment with Fetzima®. If sustained increases in blood pressure occur during Fetzima use, treatment should be discontinued or other appropriate medical interventions should be considered.

Contraindications: In those with hypersensitivity to levomilnacipran, milnacipran, or any component of the compound; In those with uncontrolled narrow-angle glaucoma; Concomitant use with MAOIs or use within 7 days of stopping treatment Fetzima®; Use of Fetzima® within 14 days of stopping an MAOI; Concomitant use of MAOIs including linezolid or intravenous methylene blue.

Manufacturer: Forest Pharmaceuticals, Inc

Analysis: Levomilnacipran, the active ingredient of Fetzima®, is a selective serotonin and norepinephrine reuptake inhibitor (SNRI). Its exact mechanism of action for use in MDD is not known; however, it is thought to be related to the potentiation of serotonin and norepinephrine in the central nervous system (CNS).

Three 8-week randomized, double-blind, placebo-controlled studies were performed to assess the safety and efficacy of levomilnacipran in adults diagnosed with MDD. Study 1 (N=713) and Study 2 (N=562) were fixed-dose studies, while Study 3 (N=434) was a flexible-dose study. The primary endpoint was the improvement of depressive symptoms as measured by the Montgomery-Asberg Depression Rating Scale (MADRS) total score. In all 3 studies, Fetzima® was statistically superior over placebo for the improvement of symptoms. In Study 1, the placebo-subtracted difference in MADRS score was -3.2 for the 40mg dose, -4.0 for the 80mg dose, and -4.9 for the 120mg dose. In Study 2, the placebo-subtracted difference in MADRS score was -3.3 with the 40mg dose and -3.1 with the 80mg dose. In Study 3, the placebo-subtracted difference in MADRS score was -3.1for the flexible-dose group of 40-120mg per day. Additionally, Fetzima® was also superior to placebo as measured by improvement in the Sheehan Disability Scale (SDS) functional impairment total score.

There is no evidence at this time to support that Fetzima® is more efficacious or safer than the currently available, more cost effective medications. Therefore, it is recommended that Fetzima® remain non-preferred and be available to the few who are unable to tolerate any preferred medications.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☐ **Preferred with Conditions**

References

[1] Fetzima [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc, a subsidiary of Forest Laboratories, Inc; 2013.