Levomilnacipran (Fetzima®)

**Indication:** Indicated for the treatment of major depressive disorder (MDD), FDA approved July 2013.

**Mechanism of action**
- Levomilnacipran, the more active enantiomer of racemic milnacipran, is a selective SNRI with greater potency for inhibition of norepinephrine relative to serotonin reuptake.
- Compared with duloxetine or venlafaxine, levomilnacipran has over 10-fold higher selectivity for norepinephrine relative to serotonin reuptake inhibition.
- The exact mechanism of the antidepressant action of levomilnacipran is unknown.

**Dosage and administration**
- Initial: 20 mg once daily for 2 days and then increased to 40 mg once daily. The dosage can be increased by increments of 40 mg at intervals of two or more days.
- Maintenance: 40-120 mg once daily with or without food. Fetzima should be swallowed whole (capsule should not be opened or crushed).
- Levomilnacipran and its metabolites are eliminated primarily by renal excretion.
  - Renal impairment Dosing:
    - Clcr 30-59 mL/minute: 80 mg once daily.
    - Clcr 15-29 mL/minute: 40 mg once daily.
    - End-stage renal disease (ESRD): Not recommended.

**Discontinuing treatment:** Gradually taper dose, if intolerable withdrawal symptoms occur, consider resuming the previous dose and/or decrease dose at a more gradual rate.

**How supplied:** Capsule ER 24 Hour
- Fetzima Titraton: 20 & 40 mg (28 ea).
- Fetzima: 20 mg, 40 mg, 80 mg, 120 mg.

**Warnings and Precautions**
- Elevated Blood Pressure and Heart Rate: measure heart rate and blood pressure prior to initiating treatment and periodically throughout treatment.
- Narrow-angle glaucoma: may cause mydriasis. Use caution in patients with controlled narrow-angle glaucoma.
- Urinary hesitancy or retention: advise patient to report symptoms of urinary difficulty.
- Discontinuation Syndrome.
- Seizure disorders: Use caution with a previous seizure disorder (not systematically evaluated).
- Risk of Serotonin syndrome when taken alone or co-administered with other serotonergic agents (including triptans, tricyclics, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John’s Wort).
- May increase the risk of bleeding particularly if used with aspirin, NSAIDs, warfarin or other anticoagulants.
- Activation of Mania/Hypomania can occur with antidepressant treatment (screen patients for bipolar disorder).
- SIADH and hyponatremia.

**Black Box Warnings:** Suicidal thoughts and behaviors. Not approved for use in pediatric patients.

References available upon request.

January 27, 2014.
Contraindications
- Hypersensitivity to levomilnacipran or any component of the formulation
- Serotonin syndrome and MAOIs
- Uncontrolled narrow-angle glaucoma

Adverse Reactions
- AEs occurring in ≥5% and at least twice the rate of placebo: Nausea, constipation, hyperhidrosis, heart rate increase, erectile dysfunction, tachycardia, vomiting, and palpitations
- AEs occurring in ≥2% of patients and at least twice the rate of placebo (table below)

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

\* Tachycardia also includes: sinus tachycardia and postural orthostatic tachycardia syndrome
\( ^{3} \) Percentage is relative to the number of patients in the associated demographic sex category. Fewer than 2% of FETZIMA-treated MDD female patients in placebo-controlled clinical studies reported adverse events related to sexual function.
\( ^{4} \) erectile dysfunction includes: erectile dysfunction, organic erectile dysfunction and psychogenic erectile dysfunction
\( ^{5} \) testicular pain includes: testicular pain, epididymitis, and seminal vesiculitis
\( ^{6} \) ejaculation disorder includes: ejaculation disorder, ejaculation delayed, ejaculation failure, and premature ejaculation
\( ^{7} \) Heart rate increased also includes: orthostatic heart rate response increased
\( ^{8} \) Blood pressure increased also includes: blood pressure systolic increased, blood pressure diastolic increased and blood pressure orthostatic increased
\( ^{9} \) Rash also includes: rash generalized, rash maculo-papular, rash erythematous and rash macular
\( ^{10} \) Hypertension also includes: orthostatic hypertension and dizziness postural
\( ^{11} \) Hypertension also includes: labile hypertension

Pharmacokinetics
- Metabolism: Hepatic to inactive metabolites (hepatic elimination is low)
- Half-life elimination: 12 hours
- Time to peak: 6-8 hours
- Excretion: Urine (58% as unchanged drug)

DDI: Strong CYP3A4 inhibitors such as ketoconazole: Do not exceed 80 mg once daily
Use in specific populations
- Pregnancy Category C: May cause fetal harm based on animal data
- Not evaluated for use in pediatric patients
- Geriatric Use: No dose adjustment recommended

Formulary status: PA required
Please contact BHRS Pharmacy Services for additional information