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:
      Cl_{cr} 30-59 mL/minute: 80 mg once daily
      Cl_{cr} 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 Titration: 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)

System Organ Class *Preferred Term*	*Placebo* *(N =1040)* *%*	*FETZIMA* *40-120 mg/d* *(N = 1583)* *%*
Gastrointestinal disorders		
Nausea	6	17
Constipation	3	9
Vomiting	1	5
Cardiac disorders		
Tachycardia[a]	2	6
Palpitations	1	5
Reproductive system and breast disorders[b]		
Erectile dysfunction[c]	1	6
Testicular pain[d]	<1	4
Ejaculation disorder[e]	<1	5
Investigations		
Heart rate increased[f]	1	6
Blood pressure increased[g]	1	3
Renal and urinary disorders		
Urinary hesitation	0	4
Skin and subcutaneous tissue disorders		
Hyperhidrosis	2	9
Rash[h]	0	2
Vascular disorders		
Hot flush	1	3
Hypotension[i]	1	3
Hypertension[j]	1	3
Metabolism and nutrition disorders		
Decreased appetite	1	3

[a] Tachycardia also includes: sinus tachycardia and postural orthostatic tachycardia syndrome
[b] 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.
[c] erectile dysfunction includes: erectile dysfunction, organic erectile dysfunction and psychogenic erectile dysfunction
[d] testicular pain includes: testicular pain, epididymitis, and seminal vesiculitis
[e] ejaculation disorder includes: ejaculation disorder, ejaculation delayed, ejaculation failure, and premature ejaculation
[f] Heart rate increased also includes: orthostatic heart rate response increased
[g] Blood pressure increased also includes: blood pressure systolic increased, blood pressure diastolic increased and blood pressure orthostatic increased
[h] Rash also includes: rash generalized, rash maculo-papular, rash erythematous and rash macular
[i] Hypotension also includes: orthostatic hypotension and dizziness postural
[j] 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

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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

References available upon request
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