LEVOMILNACIPRAN (Fetzima) Fact Sheet

Bottom Line:
Levomilnacipran is an enantiomer of milnacipran (Savella), which is an SNRI approved in the US for fibromyalgia and in other countries for depression. Levomilnacipran is effective for depression, but its tendency to cause nausea, need for titration, and urinary effects make it a second-line SNRI after venlafaxine or duloxetine. It is the most adrenergic of all the SNRIs, which may explain its high side effect potential.

FDA Indications:
Major depression.

Off-Label Uses:
Fibromyalgia; anxiety disorders; vasomotor symptoms of menopause; diabetic peripheral neuropathy; chronic musculoskeletal pain.

Dosage Forms:
ER capsules: 20 mg, 40 mg, 80 mg, 120 mg.

Dosage Guidance:
Start 20 mg QD; increase to 40 mg QD after two days, then by increments of 40 mg/day every two or more days to max 120 mg QD.

Monitoring: Periodic blood pressure and pulse.

Cost: $$$$

Side Effects:
- Most common: Nausea, vomiting, constipation, sweating, increased heart rate (7–9 beats/minute), erectile dysfunction, and urinary hesitation.
- Serious but rare: Urinary retention; increased blood pressure and tachycardia possible.
- Pregnancy/breastfeeding: Not enough data to recommend.

Mechanism, Pharmacokinetics, and Drug Interactions:
- Serotonin and norepinephrine reuptake inhibitor.
- Metabolized primarily through CYP3A4; t ½: 12 hours.
- Avoid use with MAOIs, other serotonergic medications. Use lower doses (no more than 80 mg/day) in presence of potent 3A4 inhibitors (eg, ketoconazole).

Clinical Pearls:
- Three eight-week studies showed greater efficacy than placebo at doses of 40 mg/day and greater. No head-to-head studies versus other antidepressants are available to date.
- According to the manufacturer, levomilnacipran has greater potency for norepinephrine reuptake inhibition than for serotonin reuptake inhibition.
- Noradrenergic effects may contribute to urinary hesitation or retention in 4%–6% of patients and is dose related.
- Nausea may be severe for many patients, especially early in treatment. Start 20 mg/day and titrate slowly to minimize, as patients may develop tolerance.
- Do not cut, crush, chew, or dissolve; swallow tablets whole with fluid.

Fun Facts:
Milnacipran is the parent compound of levomilnacipran and is a 50-50 racemic mix of levo- and dextro-milnacipran. Due to placebo-controlled studies showing efficacy, it has been approved for depression in 45 countries worldwide. However, since it was reaching the end of its patent life, the manufacturer did not submit it for FDA approval in the US, opting instead to isolate the l-isomer for testing and ultimate FDA approval. Fetzima enjoys market exclusivity until 2023.