LEVOMILNACIPRAN

**THERAPEUTICS**

**Brands** • Fetzima  
*see index for additional brand names*

**Generic?** No

**Class**
- Neuroscience-based Nomenclature: serotonin, norepinephrine reuptake inhibitor (SN-RI)
- SNRI (dual serotonin and norepinephrine reuptake inhibitor); antidepressant

**Commonly Prescribed for**  
(bold for FDA approved)  
- Major depressive disorder  
- Fibromyalgia  
- Neuropathic pain/chronic pain

**How the Drug Works**
- Boosts neurotransmitters serotonin, norepinephrine/noradrenaline, and dopamine  
- Blocks norepinephrine reuptake pump (norepinephrine transporter), presumably increasing noradrenergic neurotransmission  
- Blocks serotonin reuptake pump (serotonin transporter), presumably increasing serotonergic neurotransmission  
- Presumably desensitizes both serotonin 1A receptors and beta adrenergic receptors  
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, levomilnacipran can increase dopamine neurotransmission in this part of the brain

**How Long Until It Works**
- Onset of therapeutic actions is usually not immediate, but often delayed 2–4 weeks  
- If it is not working within 6 or 8 weeks, it may require a dosage increase (off label), or it may not work at all  
- May continue to work for many years to prevent relapse of symptoms

**If It Works**
- The goal of treatment of depression is complete remission of current symptoms as well as prevention of future relapses  
- Treatment of depression most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped  
- Continue treatment of depression until all symptoms are gone (remission) or significantly reduced  
- Once symptoms gone, continue treating for 1 year for the first episode of depression  
- For second and subsequent episodes of depression, treatment may need to be indefinite

**If It Doesn’t Work**
- Many depressed patients only have a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)  
- Other depressed patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory  
- Some depressed patients who have an initial response may relapse even though they continue treatment, sometimes called “poop-out”  
- Consider increasing dose, switching to another agent, or adding an appropriate augmenting agent  
- Consider psychotherapy  
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)  
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and switch to a mood stabilizer

**Best Augmenting Combos for Partial Response or Treatment Resistance**
- Augmentation experience is limited compared to other antidepressants  
- Benzodiazepines can reduce insomnia and anxiety  
- Bupropion, mirtazapine, reboxetine, or atomoxetine (use combinations of antidepressants with caution as this may activate bipolar disorder and suicidal ideation)  
- Modafinil, especially for fatigue, sleepiness, and lack of concentration  
- Mood stabilizers or atypical antipsychotics for bipolar depression, psychotic depression, or treatment-resistant depression  
- Hypnotics or trazodone for insomnia
• Classically, lithium, buspirone, or thyroid hormone

Tests
• Check heart rate and blood pressure before initiating treatment and regularly during treatment

Best Augmenting Agents for Side Effects
★ For urinary hesitancy, give an alpha 1 blocker such as tamsulosin or naftopidil
• Often best to try another antidepressant monotherapy prior to resorting to augmentation strategies to treat side effects
• Trazodone or a hypnotic for insomnia
• Bupropion, sildenafil, vardenafil, or tadalafil for sexual dysfunction
• Benzodiazepines for anxiety, agitation
• Mirtazapine for insomnia, agitation, and gastrointestinal side effects
• Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
• Activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer, or an atypical antipsychotic, and/or discontinuation of levomilnacipran

DOSING AND USE

Usual Dosage Range
• 40–120 mg once daily

Dosage Forms
• Extended-release capsule 20 mg, 40 mg, 80 mg, 120 mg

How to Dose
• Initial dose 20 mg once daily for 2 days, then increase to 40 mg once daily; can increase by 40 mg/day every 2 or more days; maximum recommended dose 120 mg once daily

Dosing Tips
• Can be taken with or without food
• Do not break or chew levomilnacipran capsules, as this will alter controlled-release properties
• If intolerable anxiety, insomnia, agitation, akathisia, or activation occur either upon dosing initiation or discontinuation, consider the possibility of activating a bipolar disorder and switch to a mood stabilizer or an atypical antipsychotic

**Overdose**
• No fatalities have been reported; experience is limited

**Long-Term Use**
• Has not been evaluated in controlled studies, but long-term treatment of major depressive disorder is generally necessary

**Habit Forming**
• No

**How to Stop**
• Taper is prudent, but usually not necessary

**Pharmacokinetics**
• Metabolized by CYP450 3A4; renally excreted
• Terminal elimination half-life approximately 12 hours

**Drug Interactions**
• Tramadol increases the risk of seizures in patients taking an antidepressant
• Can cause a fatal “serotonin syndrome” when combined with MAOIs, so do not use with MAOIs or for at least 14 days after MAOIs are stopped
• Do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing levomilnacipran
• Strong CYP450 3A4 inhibitors, such as ketoconazole, can increase plasma levels of levomilnacipran; do not exceed 80 mg once daily of levomilnacipran if used with a strong CYP450 3A4 inhibitor
• Alcohol may interact with the extended-release properties of levomilnacipran, causing a pronounced accelerated drug release (“drug dumping”); thus, taking levomilnacipran with alcohol is not recommended
• Possible increased risk of bleeding, especially when combined with anticoagulants (e.g., warfarin, NSAIDs)
• Switching from or addition of other norepinephrine reuptake inhibitors should be done with caution, as the additive pro-noradrenergic effects may enhance therapeutic actions in depression, but also enhance noradrenergically mediated side effects

**Other Warnings/Precautions**
• Use with caution in patients with history of seizures
• Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
• Use with caution in patients with controlled angle-closure glaucoma
• Not approved in children, so when treating children off label, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of non-treatment with antidepressants and make sure to document this in the patient’s chart
• Distribute the brochures provided by the FDA and the drug companies
• Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
• Monitor patients for activation of suicidal ideation, especially children and adolescents

**Do Not Use**
• If patient has uncontrolled angle-closure glaucoma
• If patient is taking an MAOI
• If there is a proven allergy to levomilnacipran or milnacipran

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**SPECIAL POPULATIONS**

**Renal Impairment**
• Maximum dose 80 mg once daily for moderate impairment
• Maximum dose 40 mg once daily for severe impairment

**Hepatic Impairment**
• Dose adjustment not necessary

**Cardiac Impairment**
• Not systematically evaluated in patients with cardiac impairment
• Drug should be used with caution
Elderly

- Some patients may tolerate lower doses better
- Reduction in risk of suicidality with antidepressants compared to placebo in adults age 65 and older

Children and Adolescents

- Safety and efficacy have not been established
- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient’s chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and strongly consider informing parents or guardian of this risk so they can help observe child or adolescent patients

Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Not generally recommended for use during pregnancy, especially during first trimester
- Nonetheless, continuous treatment during pregnancy may be necessary and has not been proven to be harmful to the fetus
- At delivery there may be more bleeding in the mother and transient irritability or sedation in the newborn
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients, this may mean continuing treatment during pregnancy
- Exposure to serotonin reuptake inhibitors early in pregnancy may be associated with increased risk of septal heart defects (absolute risk is small)
- Use of serotonin reuptake inhibitors beyond the 20th week of pregnancy may be associated with increased risk of pulmonary hypertension in newborns, although this is not proven
- Exposure to serotonin reuptake inhibitors late in pregnancy may be associated with increased risk of gestational hypertension and preeclampsia
- Neonates exposed to SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding; reported symptoms are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome, and include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying

Breast Feeding

- Unknown if levomilnacipran is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- If child becomes irritable or sedated, breast feeding or drug may need to be discontinued
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstated late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients, this may mean continuing treatment during breast feeding
reuptake blockade, but this is of unclear clinical significance as a differentiating feature from other SNRIs, although it might contribute to theoretical effects in fibromyalgia and chronic pain

* Potent noradrenergic actions may account for possibly higher incidence of sweating and urinary hesitancy than some other SNRIs

• Urinary hesitancy more common in men than women and in older men than in younger men
• Alpha 1 antagonists such as tamsulosin or naftopidil can reverse urinary hesitancy or retention
• Alpha 1 antagonists given prophylactically may prevent urinary hesitancy or retention in patients at higher risk, such as elderly men with borderline urine flow
• Nonresponse to levomilnacipran in elderly may require consideration of mild cognitive impairment or Alzheimer disease

### Potential Advantages

- Patients with depression may have higher remission rates on SNRIs than on SSRIs
- Depressed patients with somatic symptoms, fatigue, and pain

### Potential Disadvantages

- Cost
- Patients with urologic disorders, prostate disorders
- Patients with borderline or uncontrolled hypertension
- Patients with agitation and anxiety (short-term)

### Primary Target Symptoms

- Depressed mood
- Physical symptoms

### Pearls

* Has greater potency for norepinephrine reuptake blockade than for serotonin

### Suggested Reading


Citrome L. Levomilnacipran for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antidepressant – what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? Int J Clin Pract 2013;67:1089–104.