

# Levomilnacipran for the treatment of major depressive disorder

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An SNRI with once-daily dosing, levomilnacipran decreased core symptoms of MDD and was well tolerated in clinical trials

In July 2013, the FDA approved levomilnacipran for the treatment of major depressive disorder (MDD) in adults.<sup>1</sup> It is available in a once-daily, extended-release formulation (*Table 1*).<sup>1</sup> The drug is the fifth serotonin-norepinephrine reuptake inhibitor (SNRI) to be sold in the United States and the fourth to receive FDA approval for treating MDD.

Levomilnacipran is believed to be the more active enantiomer of milnacipran, which has been available in Europe for years and was approved by the FDA in 2009 for treating fibromyalgia. Efficacy of levomilnacipran for treating patients with MDD was established in three 8-week randomized controlled trials (RCTs).<sup>1</sup>

## Clinical implications

Levomilnacipran is indicated for treating MDD in adults and is unique compared with other SNRIs because it is relatively more selective for norepinephrine reuptake inhibition (NRI) compared with serotonin reuptake inhibition (SRI).<sup>1</sup> In vitro studies demonstrate that the drug has >10-fold greater selectivity for norepinephrine reuptake inhibition than it does for serotonin reuptake inhibition, compared with duloxetine or venlafaxine.<sup>2</sup>

This difference in selectivity could lend itself to treating symptoms of MDD that might be related to norepinephrine deficiency; these include decreased concentration, lassitude, mental and physical slowing, and decreased self-care.<sup>3,4</sup> Some authors claim that individual patients could experience improvement in their so-

**Table 1**

## Levomilnacipran: Fast facts

<b>Brand name:</b> Fetzima
<b>Class:</b> Serotonin-norepinephrine reuptake inhibitor
<b>Indication:</b> Treatment of major depressive disorder in adults
<b>FDA approval date:</b> July 26, 2013
<b>Availability date:</b> Fourth quarter of 2013
<b>Manufacturer:</b> Forest Pharmaceuticals
<b>Dosage forms:</b> Extended-release capsules in 20 mg, 40 mg, 80 mg, and 120 mg strengths
<b>Recommended dosage:</b> 40 mg to 120 mg capsule once daily with or without food
<b>Source:</b> Reference 1

cial and occupational functioning in addition to improvement in the core symptoms of depression.<sup>5</sup>

Levomilnacipran is the more active enantiomer of milnacipran, an SNRI that is approved for treating fibromyalgia in the United States and approved for treating depression in many other countries.<sup>6</sup> In general, enantiomeric formulations are believed to have advantages over racemic formulations because they are less com-

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### Disclosures

Dr. Macaluso has been the principal investigator in clinical trials for AbbVie, Eisai, Envivo, Janssen, Naurex, and Pfizer. All clinical trial and study contracts and payments were made through the Kansas University Medical Center Research Institute. Drs. Kazanchi and Malhotra report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

plex and have a more selective pharmacodynamic profile, better therapeutic index, lower liability for drug-drug interactions (DDIs), and a less complicated relationship between plasma concentration and pharmacodynamic effect.<sup>6</sup> In addition, regulatory guidelines in the United States recommend development of enantiomers over racemates where appropriate.<sup>7</sup>

### How it works

Levomilnacipran's exact mechanism of action is unknown. Similar to other SNRIs, it binds with high affinity to the serotonin (5-HT) and norepinephrine (NE) transporters and potently inhibits 5-HT and NE reuptake. Levomilnacipran lacks significant affinity for any other receptors, ion channels, or transporters tested *in vitro*.<sup>2</sup> It differs from other SNRIs such as venlafaxine and duloxetine in having higher selectivity for norepinephrine vs serotonin reuptake inhibition. *In vitro* studies demonstrated a 2-fold preference for NE over 5-HT reuptake inhibition.<sup>2</sup>

### Pharmacokinetics

Levomilnacipran reaches maximum plasma concentration within 6 to 8 hours of oral administration and has a half-life of approximately 12 hours, which makes it suitable for once-daily dosing. The concentration of levomilnacipran at steady state is proportional to the dosage of the drug when administered within the range of 25 to 300 mg once daily.<sup>1</sup>

The drug's mean apparent total clearance is 21 to 29 liters/hour and its bioavailability is not significantly affected when taken with food. The drug is widely distributed in the body and is converted primarily to 2 metabolites: desethyl levomilnacipran and p-hydroxy-levomilnacipran. Both metabolites are inactive and undergo further conjugation with glucuronide. The drug is eliminated primarily via renal excretion.<sup>1</sup>

The major enzyme that catalyzes metabolism of levomilnacipran is cytochrome P 450 (CYP) 3A4, which makes

it susceptible to DDIs with drugs that inhibit or induce this enzyme. For example, a person taking levomilnacipran with a potent CYP3A4 inhibitor, such as ketoconazole, may require a dosage adjustment. No dosage adjustment is needed when given with a CYP3A4 inducer or substrate. Drinking alcohol with levomilnacipran may cause more rapid release of the drug into the blood stream.<sup>1</sup>

### Efficacy

Levomilnacipran decreased core symptoms of MDD and showed a statistically significant separation from placebo in 2 phase III RCTs (*Table 2, page 54*).<sup>3,5</sup> The first study was a 10-week flexible dose (75 or 100 mg) trial in 563 outpatients age 18 to 70 who met DSM-IV-TR criteria of MDD for >1 month and had a 17-item Hamilton Depression Rating Scale (HDRS-17) score >22 and a Sheehan Disability Scale (SDS) score >10.<sup>3</sup> The primary efficacy measure was change in Montgomery-Åsberg Depression Rating Scale (MADRS) score from baseline to week 10. Secondary efficacy measures included the HDRS-17, SDS, and Clinical Global Impressions-improvement scale. Efficacy analyses included 276 subjects treated with levomilnacipran and 277 treated with placebo.<sup>3</sup>

Levomilnacipran was significantly superior to placebo on the MADRS and HDRS-17 from baseline to week 10. Response and remission rates were significantly greater for the levomilnacipran group compared with placebo. Response exceeded the 10% average advantage for drug vs placebo and 46% of levomilnacipran-treated patients achieved remission.<sup>3</sup>

The number needed to treat (NNT), based on the MADRS scores for the levomilnacipran group compared with the placebo group, was 6 for response and 5 for remission.<sup>3</sup> By comparison, most studies of venlafaxine demonstrate a NNT of 8.<sup>3</sup>

Levomilnacipran generally was reported to be safe and well tolerated. The most common adverse events leading to discon-

### Clinical Point

Levomilnacipran is suitable for once-daily dosing; maximum plasma concentration is 6 to 8 hours, and the drug has a half-life of 12 hours



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### Clinical Point

Levomilnacipran was well tolerated in clinical trials; 9% of patients who received the drug discontinued because of adverse events

tinuation in the levomilnacipran group were nausea, vomiting, change in systolic and diastolic blood pressure, and increase in heart rate. The favorable tolerability profile of levomilnacipran may relate to the 2-fold greater potency for NE reuptake inhibition compared with 5-HT reuptake inhibition.<sup>3</sup>

The second study was an 11-week, fixed-dose trial of levomilnacipran using 40, 80, or 120 mg. A total of 724 outpatients age 18 to 65 who met DSM-IV-TR criteria for MDD and who had an ongoing episode of depression lasting >8 weeks were randomly assigned to receive placebo (n = 179) or levomilnacipran at 40 mg (n = 181), 80 mg (n = 181), or 120 mg (n = 183) once daily for 8 weeks of double-blind treatment followed by a 2-week, double-blind taper of the drug.<sup>5</sup> The primary efficacy parameter was change from baseline on the MADRS and the secondary efficacy parameter was change from baseline in SDS total score. HDRS-17, CGI-I, and CGI-S were included as secondary outcome measures.<sup>5</sup>

Significant difference in MADRS total score were seen in the levomilnacipran group compared with the placebo group (least mean squared difference: 40 mg/d, -3.23; 80 mg/d, -3.99; and 120 mg/d, -4.86). Higher dosages produced a numerically greater change and significant separation from placebo occurred sooner in the 80-mg and 120-mg groups compared with the 40-mg group.<sup>5</sup>

Significant differences vs placebo were consistently observed across secondary outcome measures for the higher dosages of levomilnacipran, and improvement in SDS total score was noted in all levomilnacipran groups compared with the placebo group. When dosed at 120 mg/d, levomilnacipran produced significant improvement vs placebo on all SDS subscales and was as well tolerated as the 80 mg dosage.<sup>5</sup>

No new safety concerns were observed in the study. A dose-response relationship in tolerability was not demonstrated and

the number of patients reporting adverse events and who discontinued participation because of adverse events was higher in the 80-mg group than in the 40-mg and 120-mg groups.<sup>5</sup>

### Tolerability

Overall, levomilnacipran was well tolerated in clinical trials, during which 2,673 subjects were exposed to the drug—translating to 942 patient-years of exposure. These patients ranged in age from 18 to 78; 825 of these subjects were enrolled in long-term studies for 1 year. Dosing of levomilnacipran during these studies ranged from 40 to 120 mg once daily, without regard to food.<sup>1</sup>

Nine percent of patients who received levomilnacipran in short-term studies discontinued because of adverse events, compared with 3% of patients who received placebo. The most common adverse event reported was nausea; other common adverse events reported included constipation, hyperhidrosis, elevated heart rate, erectile dysfunction, tachycardia, palpitations, and vomiting. Of these events, only erectile dysfunction and urinary hesitation were dose-related.<sup>1</sup> Among levomilnacipran-treated female patients, <2% reported adverse events related to sexual dysfunction.

All SNRIs have well established associations with elevation in blood pressure and heart rate. Levomilnacipran resulted in a mean increase of 3 mm HG in systolic and 3.2 mm Hg in diastolic blood pressure in short-term, placebo-controlled trials.<sup>1</sup>

Orthostatic hypotension was observed in 11.6% of patients in the levomilnacipran groups, compared with 9.7% in placebo groups in all short-term studies. Orthostatic reductions of blood pressure occurred in 5.8%, 6.1%, and 9.8% of levomilnacipran-treated patients with dosages of 40, 80, and 120 mg/d, respectively, indicating a dose-dependent adverse event. A mean increase in heart rate of 7.2 beats per minute (bpm) also was seen in short-term studies in the levomilnacipran-treated group compared

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**Table 2**

**Summary of the seminal data that led to FDA approval of levomilnacipran for the treatment of MDD in adults**

	Study type	Inclusion criteria	Dosing	Efficacy assessment
Study 1 <sup>3</sup>	Phase III, RCT 10 weeks n = 557 (completers)	-Outpatient -Age 18 to 70 -Meeting DSM-IV-TR criteria for MDD for >1 month -HDRS-17 >22 -SDS >10	Flexible 75 to 100 mg/d	MADRS 0 to 10 week shows: 4.2 point difference in favor of levomilnacipran vs placebo NNT = 6 (response) NNT = 5 (remission) <sup>3</sup>
Study 2 <sup>5</sup>	Phase III RCT 11 weeks n = 704 (completers)	-Outpatient -Age 18 to 65 -Meeting DSM-IV-TR criteria for MDD for >8 weeks -MADRS >30	Fixed 40, 80, or 120 mg/d	MADRS total score: shows higher dose of levomilnacipran (80, 120 mg) lead to significantly greater changes compared with placebo

AE: adverse event; GI: gastrointestinal; HDRS: Hamilton Depression Rating Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; NNT: number needed to treat; RCT: randomized control trial; SDS: Sheehan Disability Scale

**Clinical Point**

Contraindications include hypersensitivity to levomilnacipran or milnacipran and uncontrolled narrow-angle glaucoma

with 0.3 bpm in the placebo-treated group.<sup>1</sup> Clinicians should monitor blood pressure and heart rate routinely because of potential increases seen in some subjects in these studies, which excluded those who had significant cardiovascular disease.

**Unique clinical issues**

Both in-vitro and in-vivo studies found that levomilnacipran exhibited more potency for NE reuptake inhibition than for 5-HT reuptake inhibition at the lowest effective dosage (10 mg/kg). However, as the dosage was increased (20 mg/kg and 40 mg/kg), it was equally potent at NE and 5-HT reuptake inhibition. This is in contrast to venlafaxine, which demonstrates a similar, but opposite, effect in terms of potentiation at the 5-HT and NE reuptake pumps.<sup>2</sup>

The greater noradrenergic effect of levomilnacipran could lend itself to treating certain subgroups of patients whose symptoms are believed to be related to deficiencies in NE (eg, lassitude).<sup>4</sup> This concept is theoretical, and was not explicitly studied in clinical trials and the drug is not labeled in this way.

**Contraindications**

Contraindications to levomilnacipran are similar to those seen with SSRIs and SNRIs, including concomitant use of a monoamine oxidase inhibitor (MAOI) and the use of the levomilnacipran within 14 days of stopping an MAOI. Contraindications unique to levomilnacipran include hypersensitivity to levomilnacipran, milnacipran, or any component specific to the formulation; and uncontrolled narrow-angle glaucoma.<sup>1</sup>

**Dosing**

The recommended dosage range of levomilnacipran is 40 to 120 mg once daily with or without food. The capsules should be swallowed whole and should not be opened or crushed. As with most psychotropics, levomilnacipran should be taken at approximately the same time each day.<sup>1</sup>

The manufacturer recommends an initial dose of levomilnacipran of 20 mg once daily for 2 days, increased to 40 mg once daily. Based on efficacy and tolerability, levomilnacipran can be increased in increments of 40 mg every 2 days.

**Tolerability and safety**

18 placebo and 26 levomilnacipran-treated patients withdrew because of AEs  
 Most common AE in the levomilnacipran group was GI upset

Well tolerated and safe

Dosage adjustment is recommended for patients with moderate or severe renal impairment; and the maintenance dosage should not exceed 80 mg and 40 mg, respectively, in these populations. As with many antidepressants, gradual dosage reduction is recommended to avoid discontinuation symptoms.

**References**

1. Fetzima [package insert]. St. Louis, MO: Forest Laboratories; 2013.
2. Auclair AL, Martel JC, Assié MB, et al. Levomilnacipran (F2695), a norepinephrine-preferring SNRI: profile

**Related Resources**

- 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? [published online September 8, 2013]. *Int J Clin Pract*. doi: 10.1111/ijcp.12298.
- Mago R, Forero G, Greenberg WM, et al. Safety and tolerability of levomilnacipran ER in major depressive disorder: results from an open-label, 48-week extension study. *Clin Drug Investig*. 2013;33(10):761-771.

**Drug Brand Names**

Duloxetine • Cymbalta	Milnacipran • Savella
Ketoconazole • Nizoral	Venlafaxine • Effexor
Levomilnacipran • Fetzima	

in vitro and in models of depression and anxiety. *Neuropharmacology*. 2013;70:338-347.

3. Montgomery SA, Mansuy L, Ruth A, et al. Efficacy and Safety of levomilnacipran sustained release in moderate to severe major depressive disorder: a randomized, double-blind, placebo-controlled, proof-of-concept study. *J Clin Psychiatry*. 2013;74(4):363-369.
4. Kasper S, Meshkat D, Kutzelnigg A. Improvement of the noradrenergic symptom cluster following treatment with milnacipran. *Neuropsychiatric Dis Treat*. 2011;7(suppl 1): 21-27.
5. Asnis GM, Bose A, Gommoll CP, et al. Efficacy and safety of levomilnacipran sustained release 40 mg, 80 mg, or 120 mg in major depressive disorder: a phase 3, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2013;74(3):242-248.
6. Hutt AJ, Vanetová J. The chiral switch: the development of single enantiomer drugs from racemates. *Acta Facultatis Pharmaceuticae Universitatis Comenianae*. 2003; 50(7):23.
7. U.S. Food and Drug Administration. Development of new stereoisomeric drugs. Published May 1, 1992. <http://www.fda.gov/drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122883.htm#UKHEWm4ZyYE.email>. Accessed October 8, 2013.

**Clinical Point**

The manufacturer recommends an initial dose of levomilnacipran of 20 mg once daily for 2 days, increased to 40 mg once daily

**Bottom Line**

Levomilnacipran is FDA-approved for treating major depressive disorder in adults. In 2 randomized controlled trials, the drug showed a significant separation from placebo. Levomilnacipran generally was reported to be safe and well tolerated; common adverse events were nausea, vomiting, changes in blood pressure, and an increase in heart rate.