# Levomilnacipran Pharmacokinetics in Healthy Volunteers Versus Patients with Major Depressive Disorder and Implications for Norepinephrine and Serotonin Reuptake Inhibition

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## ABSTRACT

**Purpose:** Levomilnacipran, a selective serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor, is approved for the treatment of major depressive disorder (MDD) in adults. The objectives of this investigation were to characterize the pharmacokinetic (PK) parameters of levomilnacipran in healthy subjects and in patients with MDD and to compare the plasma concentrations observed at clinically effective doses (40–120 mg daily) in MDD patients versus in vitro inhibitory concentration values for NE and 5-HT transporters.

**Methods:** Data from 2 trials were analyzed: a Phase I trial (healthy volunteers received a single dose of levomilnacipran extended-release capsule [ER; 25, 50, or 100 mg], escalating multiple doses of levomilnacipran ER [25–300 mg once daily], or placebo); and a Phase III trial (adults with MDD received a fixed dose of levomilnacipran ER [40, 80, or 120 mg once daily for 8 weeks]). Plasma samples of participants were assayed to determine levomilnacipran concentrations, and PK analyses were performed. Unbound plasma concentrations of levomilnacipran in MDD patients were estimated, and inhibitory concentration values were determined by curve fitting of the in vitro data.

**Findings:** $C_{max}$ and AUC were dose proportional after single dosing (25–100 mg) and multiple dosing (across the 25–300 mg dose range) of levomilnacipran ER in healthy subjects. Dose-proportional steady-state $C_{max}$ (93, 180, and 297 ng/mL) and $AUC_{0-\tau}$ (1520, 2935, and 4799 ng*h/mL) were also observed in patients with MDD who received levomilnacipran ER (40, 80, and 120 mg daily). $T_{max}$ was ~6 hours and was similar after single and multiple oral doses of levomilnacipran ER. Estimates of levomilnacipran concentration at 50%, 80%, and 90% inhibition were 19, 91, and 237 nM, respectively, for the 5-HT transporter, and 10, 41, and 92 nM for the NE transporter. Average unbound plasma concentrations for levomilnacipran in MDD patients treated with levomilnacipran ER 40, 80, or 120 mg daily exceeded the estimated concentration at 80% and 90% inhibition for 5-HT and NE.

**Implications:** Levomilnacipran PK was dose proportional after single and multiple dosing and was similar between healthy subjects and patients with MDD. Steady-state unbound plasma concentrations of levomilnacipran across the approved dose range (40, 80, and 120 mg daily) in MDD patients were estimated to be comparable or greater than the concentrations that inhibited reuptake of NE and 5-HT by >90% and >80%, respectively, in vitro. (*Clin Ther*. 2015;37:2059–2070) 

**Key words:** levomilnacipran, major depressive disorder, pharmacokinetics, SNRI, transporter inhibition.

## INTRODUCTION

Major depressive disorder (MDD) is a serious mental illness characterized by patients experiencing ≥1

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clinically significant depressive episode that produces significant functional impairment. Dysfunction of both the norepinephrine (NE) and serotonin (5-HT) systems has been associated with MDD etiology and pathophysiology. Anxiety, agitation, and irritability have been more closely associated with 5-HT, whereas other depressive symptoms (eg, fatigue, lack of motivation, decreased concentration) seem to be more strongly related to NE.[1–4] Although all approved serotonin NE reuptake inhibitors (SNRIs) inhibit the reuptake of NE and 5-HT, they differ in terms of their relative potencies at these transporters in vitro,[5–7] and these differences may have clinical implications.[8]

Levomilnacipran (1S, 2R-milnacipran) is an SNRI and the more active enantiomer of racemic milnacipran. In vitro studies have shown that levomilnacipran has higher affinity for both human recombinant and rat native 5-HT and NE transporters than milnacipran.[7,9] The $t_{½}$ of levomilnacipran after administration of an immediate-release formulation was 8.3 hours. To allow for once-daily administration, an extended-release (ER) formulation of levomilnacipran was developed. The ER formulation has bioavailability >90% compared with an oral solution and intravenous administration. Levomilnacipran ER* capsules were approved by the US Food and Drug Administration in July 2013 for the treatment of MDD in adults. The efficacy of levomilnacipran ER was established in 3 Phase III studies (ClinicalTrials.gov identifiers, NCT01377194, NCT01034462, and NCT00969709).[9–11] The safety of levomilnacipran ER was also evaluated in these short-term clinical trials and further supported by a 48-week open-label study (NCT01034267).[12]

Milnacipran was first approved in 1996 in France for the treatment of MDD and is currently marketed as a treatment for MDD in >45 countries but not in the United States.[13] The use of milnacipran in the treatment of fibromyalgia has been approved in the United States but not in Europe. Milnacipran studies in MDD were conducted more than a decade ago, and head-to-head Phase III studies of milnacipran and levomilnacipran in the treatment of MDD have not been conducted; as such, no valid comparison between levomilnacipran and milnacipran clinical data can be made.

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The objectives of the present investigation were to characterize the pharmacokinetic (PK) parameters of levomilnacipran in healthy subjects and in patients with MDD and to estimate NE and 5-HT reuptake inhibition in plasma at clinically effective doses (40–120 mg daily) by comparing the steady-state plasma concentrations of levomilnacipran versus the drug concentrations from a previously published in vitro reuptake inhibition study using human recombinant transporters.[7]

## SUBJECTS AND METHODS

### Study Design and Dosing

The PK variables of levomilnacipran were assessed in healthy adult volunteers after single- or multiple-dose administration of levomilnacipran ER capsules in a Phase I trial (LVM-PK-01) and in adult patients with MDD after multiple-dose administration in a Phase III trial (LVM-MD-01; ClinicalTrials.gov identifier: NCT00969709).[11] Both trials were conducted in full compliance with US Food and Drug Administration guidelines for Good Clinical Practice and the ethical principles of the Declaration of Helsinki. The study protocols were approved by the institutional review board for each study site, and all study participants provided written informed consent.

### Single-and Multiple-Escalating Oral Doses in Healthy Volunteers

LVM-PK-01 was a Phase I, single-center, randomized, double-blind, placebo-controlled, single-dose (25, 50, or 100 mg of levomilnacipran ER) and multiple-dose (25–300 mg daily of levomilnacipran ER) study in healthy volunteers. Nonsmoking men and women, aged 18 to 45 years, were eligible to enroll in the Phase I trial. Study subjects had to have a sitting pulse rate ≥50 beats/min and ≤100 beats/min at screening and a body mass index ≥18 kg/m$^2$ and ≤32 kg/m$^2$.

Subjects with the following conditions were excluded from participation in the Phase I study: known hypersensitivity to levomilnacipran or milnacipran treatments administered during studies, selective serotonin reuptake inhibitors, or other noradrenergic drugs; having a clinically significant disease or condition that might interfere with study participation or results; sitting systolic blood pressure ≤90 or ≥140 mm Hg or sitting diastolic blood pressure