Duloxetine HCl (Cymbalta) for the Treatment of Depression, Neuropathic Pain, Fibromyalgia, and Stress Urinary Incontinence

Martin P. Cruz, PharmD, CGP, Michelle E. Gonzales, PharmD, Jennifer Jacobs, PharmD, and Melinda Constante LaFave, PharmD

INTRODUCTION

Serotonin (5-HT) and norepinephrine (NE) are neurotransmitters thought to help regulate human emotions and sensitivity to pain. When these neurotransmitters are not in balance, people may become depressed and may be more likely to experience painful physical symptoms. The combination of emotional and painful physical effects of depression can have a tremendous negative impact on a person's quality of life.

Depression

Because of the potent and balanced dual action in neuronal 5-HT and NE reuptake inhibition, duloxetine HCl (DLX, Cymbalta, Eli Lilly) gained the approval of the U.S. Food and Drug Administration (FDA) for the treatment of Major Depressive Disorder (MDD) in August 2004 and diabetic peripheral neuropathic pain (DPNP) in September 2004. This product is also being investigated for the treatment of stress urinary incontinence (SUI) and fibromyalgia (FM) worldwide. The FDA is reviewing data for these two indications.

Almost 121 million people worldwide and nearly 19 million Americans experience depression each year, making it the third most costly and disabling illness in the U.S. By the year 2020, it is predicted that depressive illness will be the second leading cause of disability worldwide. Studies have revealed relapse rates between 7% and 26% (average, 20%) for patients receiving antidepressants, compared with 19% to 56% (average, 40%-50%) for patients receiving placebo. Patients whose painful physical symptoms were relieved were more likely to achieve remission of depression than those who did not receive relief from painful physical symptoms.

Emotional symptoms of MDD include sadness and anxiety. The physical presentation of depression can include nagging aches and pains, digestive problems, sleep disturbances, or emotional symptoms that persist for months after treatment. Common antidepressants affect the actions of serotonin. DLX offers an alternative to health care providers in treating and preventing relapse in depression by helping to restore the balance of both serotonin and norepinephrine. Today, only 25% to 35% of patients treated for depression in clinical studies experience relief from all of their symptoms, but this may improve with DLX therapy.

Many common antidepressants affect the actions of serotonin. DLX offers an alternative to health care providers in treating and preventing relapse in depression by helping to restore the balance of both serotonin and norepinephrine. Today, only 25% to 35% of patients treated for depression in clinical studies experience relief from all of their symptoms, but this may improve with DLX therapy.

Stress Urinary Incontinence

Another potential therapeutic use of DLX is for the treatment of moderate-to-severe SUI. DLX has already gained approval from the European Union for this indication; it is marketed as Yentreve in Greece, as Cymbalta in Italy, and as Xeristar in Spain. It is thought that SUI might respond to treatment that modulates 5-HT and NE levels. The final FDA approval for this indication is contingent upon successful completion of additional acute preclinical and clinical pharmacology studies, satisfactory resolution of manufacturing issues, and label negotiations.

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Fibromyalgia

DLX is also being studied in patients, with or without MDD, for its safety and efficacy in the treatment of fibromyalgia (FM). FM is a chronic, incapacitating musculoskeletal disorder characterized by widespread body pain and muscle tenderness. It is often accompanied by headaches, sleep disturbances, and fatigue.17

In a study by Arnold et al. that compared DLX with placebo for the treatment of FM, DLX provided relief for women with FM.18 DLX seems to improve the disorder more significantly in women than in men, but the numbers of men in the studies were not large enough to extrapolate these data to the general population.

CHEMISTRY AND PHARMACOLOGY

DLX is chemically designated as (+)-(S)-N-methyl-γ-(1-naphthylxoy)-2-thiophenepropylamine HCl. Its empirical formula is C_{34}H_{40}NOS·HCl, and its molecular weight is 333.88. It is a white/brown-white solid that is slightly soluble in water (Figure 1).19

According to its manufacturer, the antidepressant and pain inhibitory actions of DLX are related to its inhibition of neuronal 5-HT and NE reuptake, which potentiates serotonergic and noradrenergic activity in the central nervous system (CNS).20 Both 5-HT and NE play important roles in regulating mood and are known for their involvement in the descending pain pathways that inhibit afferent pain fibers ascending through the spinal cord.20 Increasing neurotransmission of both 5-HT and NE may offer better antidepressant efficacy than potentiation of a single neurotransmitter.21 This regulatory system may also help alleviate painful physical symptoms associated with depression (Figure 2).

Pain signals may be inhibited in the spinal cord by gamma-aminobutyric acid (GABA) and glycine (in the segmental level) and inhibited in the descending pathways of the spinal cord by 5-HT and NE (in the supraspinal level). DLX may exert an analgesic effect via reuptake blockade of 5-HT and NE in the brain and spinal cord, modulating pain perception without changing the underlying pathophysiology of the affected nerves.20

This is the rationale for the efficacy of DLX in the treatment of DPNP.

DLX lacks significant affinity for muscarinic, histamine_1, alpha_1-adrenergic, alpha_2-adrenergic, dopamine_1, 5-HT_1A, 5-HT_1D, 5-HT_2A, 5-HT_2C, and opioid receptors.22-25 It does not inhibit the enzyme monoamine oxidase (MAO). DLX has increased neural sphincter activity and bladder capacity in animal studies and has been investigated in urinary incontinence.26,27

PHARMACOKINETICS

The pharmacokinetic profile of DLX, a delayed-release formulation, has been studied in healthy volunteers, in older people, and in patients with renal and hepatic impairment. Each capsule contains enteric-coated pellets of the active drug to prevent its degradation in the stomach’s acidic environment.

In healthy volunteers, the elimination half-life of DLX is about 12 hours (range, 8 to 17 hours) or 11 to 16 hours in some studies.24,28,29 Steady-state plasma concentrations are achieved in three days; the volume of distribution (V_d) is about 1,640 liters. More than 90% of the drug is protein-bound, primarily to albumin and alpha_1-acid glycoprotein.

DLX is well absorbed orally, with a median two-hour lag time until absorption begins (T lag). The maximum plasma concentration (C_{max}) is achieved at six hours after the dose is given. Because food does not significantly affect the absorption of DLX, the drug can be taken without regard to meals.

Elimination of DLX is primarily through hepatic metabolism, which involves cytochrome P450 isoenzymes CYP2D6 and CYP1A2. Biotransformation pathways involve oxidation of the naphthyl ring, followed by conjugation and further oxidation. Major metabolites found in plasma include 4-hydroxy DLX glucuronide and 5-hydroxy, 6-methoxy DLX sulfate. Most of the DLX dose appears in the urine as metabolites (about 70%); approximately 20% is found in the feces. Only trace amounts (less than 1% of the dose) of unchanged DLX are present in the urine.20

Main comparators of DLX in the treatment of MDD are venlafaxine (Effexor, Wyeth), fluoxetine (Prozac, Pfizer), sertraline (Zoloft, Pfizer), paroxetine (Paxil, GlaxoSmithKline), escitalopram (Lexapro, Forest), citalopram (Cymbalta, Forest), and bupropion (Wellbutrin, GlaxoSmithKline). The pharmacokinetic and pharmacological profiles of these agents are summarized in Table 1.19
Major Depressive Disorder

Detke et al.30

In a multicenter, double-blind, placebo-controlled, parallel-group study, DLX 60 mg/day once daily was superior to placebo in the treatment of MDD and its associated painful physical symptoms. All adult patients with MDD met criteria as outlined in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). The patients were assigned to receive placebo (n = 122) or DLX 60 mg/day (n = 123) for nine weeks.

The authors measured painful symptoms using the Clinical Global Impressions–Severity (CGI–S) Scale, the Patient Global Impressions–Improvement (PGI–I) Scale, and the Quality-of-Life in Depression Scale (QLDS). Designed with a power of 80% and an alpha set at 0.05, the estimated sample size was 240 patients.

The primary efficacy measure was the Hamilton Rating Scale for Depression (HAM–D–17) total score.

Patients receiving DLX showed significant improvement (P < .001), compared with those taking placebo beginning at two weeks after randomization. This improvement in relieving depressive symptoms continued until the end of the treatment.

At nine weeks, the DLX patients also showed significantly greater estimated probabilities of response (P < .001) and remission (P < .001) than the placebo group. The patients evaluated in this study were primarily white women (mean age, 42 years).

The most frequently reported ADE in the first week was nausea (80%), but this tended to subside after a median of seven days. Abnormal ejaculations in three patients, rash in two, migraine in two, and somnolence in two resulted in discontinuation of the study for the affected patients.

Most patients (85.4%) tolerated the 60-mg/day dose without a temporary dose reduction. The incidence of hypertension was also monitored (in one DLX-treated patient and no placebo-controlled patients); the difference was not significant (P = 1.0).

Weight gain was not clinically significant. The DLX patients lost a mean of 1.68 pounds, compared with the placebo patients (P = .005).

A 52-week, 52-site, multinational, single-arm, placebo-controlled, open-label trial was designed to evaluate DLX for patients 65 years of age or older (n = 101) with MDD. The data were obtained from a larger study involving patients 18 years of age or older (n = 1,279) who met the DSM-IV criteria for MDD. Patients had to have scored 3 or higher on the CGI–S Scale at the screening visit and at the baseline evaluation.

The primary endpoint was efficacy, as assessed by the CGI–S Scale at every visit. Other efficacy endpoints included scores on the HAM–D–17, the Beck Depression Inventory–II (BDI–II), the CGI–I at every visit, and the Sheehan Disability Scale (SDS). All efficacy endpoints were assessed at 6, 28, and 52 weeks unless otherwise noted. Safety endpoints collected at each visit included discontinuation rates; the reporting of ADEs; and changes from baseline in vital signs, electrocardiograms (ECGs), and laboratory values.

At week 52, the mean changes from baseline scores were as follows:

- CGI–S score, −3.15 (P = .12)
- PGI–I score, 1.84 (P = .16)
- HAM–D–17 total score, −17.5 (P = .8)
- BDI–II score, −22.0 (P = 1.1)
- SDS–work score, −4.27 (P = .39)
- SDS–family score, −4.95 (P = .37)
- SDS–social score, −4.85 (P = .40)

Data for the primary efficacy endpoints were also compared with those for younger adults. No statistical differences were observed between the groups (P ≥ .05).

Adverse effects experienced by more than 10% of the treated subjects included dizziness, nausea, constipation, somnolence, insomnia, dry mouth, diarrhea, headache, and hyperhidrosis; 75% of these ADEs were mild to moderate. The highest rates of ADEs occurred during the first eight weeks of treatment, but the occurrence of ADEs decreased over time. Of note, two patients experienced a fall, one patient reported a syncopal event, and one patient experienced postural hypotension.

The authors concluded that DLX therapy resulted in few cardiovascular ADEs and little change in weight. They considered DLX a valid, long-term treatment option for MDD and equally effective and tolerable in both older and younger adults.

Goldstein et al.32

An eight-week, multicenter, double-blind, placebo-controlled study enrolled 173 patients, from 18 to 65 years of age, with a current diagnosis of MDD, as specified by the DSM-IV criteria. Seventy patients took placebo, 70 took DLX 40–60 mg twice daily, and 33 took fluoxetine 20 mg daily. The patients were primarily white women, approximately 40 years of age.

The primary efficacy measure was the HAM–D–17 total score. Secondary efficacy measures included the Montgomery–Asberg Depression Rating Scale, the CGI–S, Clinical Global Impressions–Improvement (CGI–I), and the PGI–I. DLX proved superior to placebo (P = .009) in reducing MDD symptoms based on mean changes in HAM–D–17 scores from baseline to week eight. Fluoxetine was present as a qualitative control arm for detecting efficacy and was not compared with DLX. The estimated probability of remission after eight weeks of treatment with DLX (66%) was significantly greater than with placebo (32%) (P = .022).

From the mean change (last-observation-carried-forward) analysis of variance, remission rates were 27% with placebo, 43% with DLX (P = .072), and 30% with fluoxetine (P = .815). DLX was also associated with significantly improved HAM–D–17 anxiety subscale scores, compared with fluoxetine (P = .041), and it was superior to fluoxetine in all primary and most secondary efficacy outcome measures.

The most significant ADEs were asthenia (in 17.1% of patients using DLX vs. 4.3% of patients taking placebo) and insomnia (20% with DLX vs. 7.1% with placebo) (P ≤ .05).

During the active-treatment phase, discontinuation rates were 34.3% with placebo (in 24 patients), 34.3% with DLX (in 24 patients), and 36.4% with fluoxetine (in 12 patients). Only one treatment-emergent ADE—abnormal dreams—was reported, but this did not differ significantly with placebo (P = .56).

These findings suggested that DLX was efficacious, safe, and well tolerated for patients with MDD.

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<tr>
<th>Clinical Pharmacology</th>
<th>Mechanism of action</th>
<th>Available formulations and indicated strengths</th>
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<tbody>
<tr>
<td>Duloxetine HCl (Cymbalta)</td>
<td>Inhibition of CNS neuronal reuptake of serotonin and norepinephrine</td>
<td>Capsules contain 20, 30, or 60 mg of duloxetine.</td>
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<tr>
<td>Venlafaxine HCl (Effexor XR)</td>
<td>Inhibition of CNS neuronal reuptake of serotonin</td>
<td>Extended-release capsules contain 37.5, 75, or 150 mg of venlafaxine HCl.</td>
</tr>
<tr>
<td>Fluoxetine HCl (Prozac)</td>
<td>Inhibition of CNS neuronal reuptake of serotonin</td>
<td>Pulvules contain 10, 20, or 40 mg; tablets contain 10 mg; and oral suspension contains 20 mg per 5 ml of fluoxetine HCl. Weekly capsule contains 90 mg of fluoxetine HCl.</td>
</tr>
<tr>
<td>Sertraline HCl (Zoloft)</td>
<td>Inhibition of CNS neuronal reuptake of serotonin</td>
<td>Tablets contain 25, 50, or 100 mg of sertraline HCl.</td>
</tr>
<tr>
<td>Paroxetine HCl (Paxil)</td>
<td>Inhibition of CNS neuronal reuptake of serotonin</td>
<td>Tablets contain 10, 20, 30, or 40 mg of paroxetine HCl.</td>
</tr>
<tr>
<td>Escitalopram oxalate (Lexapro)</td>
<td>Inhibition of CNS neuronal reuptake of serotonin</td>
<td>Tablets contain 10 or 20 mg of escitalopram oxalate.</td>
</tr>
<tr>
<td>Citalopram hydrobromide (Celexa)</td>
<td>Inhibition of CNS neuronal reuptake of serotonin</td>
<td>Tablets contain 10, 20, or 40 mg of citalopram HBr.</td>
</tr>
<tr>
<td>Bupropion HCl (Wellbutrin XL)</td>
<td>Mediated by noradrenergic and/or dopaminergic mechanisms</td>
<td>Extended-release tablets contain 150 and 300 mg of bupropion HCl. Tablets contain 100, 150, or 200 mg of bupropion HCl.</td>
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### Pharmacokinetics

<table>
<thead>
<tr>
<th>Absorption</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; 6 hours post dose</th>
<th>At least 92% absorption of single dose</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; 6 to 8 hours post dose</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; 4.5 to 8.4 hours post dose</th>
<th>Complete absorption after oral dosing of HCl salt</th>
<th>Mean T&lt;sub&gt;max&lt;/sub&gt; reached 5 ± 1.5 hours post dose</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; about 4 hours post dose</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; within 5 hours of dose</th>
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<tbody>
<tr>
<td>Food effects</td>
<td>Food does not affect C&lt;sub&gt;max&lt;/sub&gt;, but delays time to reach C&lt;sub&gt;max&lt;/sub&gt; from 6 to 10 hours; decreases extent of absorption (AUC) by 10%</td>
<td>Food does not affect bioavailability of venlafaxine or its active metabolite, ODV.</td>
<td>Food does not affect systemic bioavailability but may delay absorption by 1 to 2 hours.</td>
<td>When given with food, C&lt;sub&gt;max&lt;/sub&gt; was 25% greater and T&lt;sub&gt;max&lt;/sub&gt; decreased from 8 hours post dose to 5.5 hours.</td>
<td>When administered with food, C&lt;sub&gt;max&lt;/sub&gt; was 29% greater and T&lt;sub&gt;max&lt;/sub&gt; decreased from 6.4 hours post dosing to 4.9 hours.</td>
<td>Absorption not affected by food</td>
<td>Absorption not affected by food</td>
<td>When given with food, C&lt;sub&gt;max&lt;/sub&gt; and AUC were 11% and 17% greater, respectively. Food does not affect C&lt;sub&gt;max&lt;/sub&gt; or AUC at the 300-mg XL formulation.</td>
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</table>

ALT = alanine transaminase; AST = aspartate transaminase; AUC = area under the curve; BP = blood pressure; C<sub>max</sub> = maximum concentration; CNS = central nervous system; CPK = creatine phosphokinase; CrCl = creatinine clearance; CYP = cytochrome; DCT = desmethyl-citalopram; DDCT = didesmethyl-citalopram; ESRD = end-stage renal disease; HBr = hydrobromide; HCl = hydrochloride; HTN = hypertension; LV = left ventricular; mm Hg = millimeters of mercury; N/A = not applicable; ODV = O-desmethyl venlafaxine; T<sub>max</sub> = time to maximum concentration; XL = extended release.

These data are not based on head-to-head comparisons. No conclusions regarding the comparative efficacy or safety of these products can be drawn based upon these data. All information for product comparison is from the respective product package inserts.

Adapted from Cymbalta, Managed Care Dossier, September 2004.
<table>
<thead>
<tr>
<th>Term</th>
<th>Duloxetine HCl</th>
<th>Venlafaxine HCl</th>
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<th>Paroxetine HCl</th>
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<th>Citalopram hydrobromide</th>
<th>Bupropion HCl</th>
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<tbody>
<tr>
<td><strong>Metabolism</strong></td>
<td>Via CYP2D6 and CYP1A2</td>
<td>Extensively metabolized to numerous metabolites. Two major metabolites found in plasma and urine: glucuronide conjugate of 4-hydroxy duloxetine and sulfate conjugate of 5-hydroxy, 6-methoxy duloxetine</td>
<td>Via CYP2D6</td>
<td>Extensively sys-temic metabolism in liver, primarily to ODV, but also to N-desmethyl venlafaxine, N,O-didesmethyl venlafaxine, and other minor metabolites</td>
<td>Via CYP1A2</td>
<td>Extensively first-pass metabolism. The principal initial pathway of metabolism for sertraline is N-demethylation.</td>
<td>Via CYP3A4 and CYP2C19</td>
<td>Metabolized to S-DCT and S-DDCT</td>
</tr>
<tr>
<td><strong>Half-life of active ingredient</strong></td>
<td>8 to 17 hours</td>
<td>5 (±2) hours</td>
<td>1 to 3 days after acute administration and 4 to 6 days after chronic administration</td>
<td>26 hours</td>
<td>21 hours</td>
<td>27–32 hours</td>
<td>35 hours</td>
<td>21 (±9) hours</td>
</tr>
<tr>
<td><strong>Volume of distribution</strong></td>
<td>Average $V_d$ is 1,640 L</td>
<td>&gt; 90% bound to serum proteins, primarily to albumin and alpha$_1$-acid glycoprotein</td>
<td>27% of venlafaxine and 30% of ODV bound to plasma proteins</td>
<td>94.5% bound to serum proteins, including albumin and alpha$_1$-glycoprotein</td>
<td>98% bound to serum proteins</td>
<td>$V_d$ (citalopram) about 12 L/kg</td>
<td>$V_d$ data on escitalopram unavailable</td>
<td>$V_d$ (citalopram) about 12 L/kg</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>&lt; 1% of unchanged duloxetine present in urine; about 70% of dose recovered in urine as metabolites; approximately 20% recovered in feces</td>
<td>Within 48 hours of dose: approximately 87% recovered in the urine as either unchanged venlafaxine (5%), unconju-gated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%)</td>
<td>Primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted as urine.</td>
<td>Nine days post dose: about 40% to 45% recovered in urine, but unchanged sertraline not detectable in urine; 40% to 45% eliminated in feces, including 12% to 14% unchanged sertraline</td>
<td>10 days post dose: approximately 64% excreted in urine: 2% as parent compound, 62% as metabolites; about 36% excreted in feces, mostly as metabolites and less than 1% as parent compound</td>
<td>7% of oral clearance due to renal function; 8% and 10% of drug recovered in urine as escitalopram and S-DCT, respectively</td>
<td>10% and 5% of IV-administered drug recovered in urine as citalopram and DCT, respectively</td>
<td>87% and 10% of dose recovered in the urine and feces, respectively; 5% unchanged bupropion HCl</td>
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Table continues
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<tr>
<th>Special Populations</th>
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<tbody>
<tr>
<td><strong>Age</strong></td>
<td>No difference in C\textsubscript{max} between healthy, older women (65 to 77 years) and healthy, middle-aged women (32 to 50 years), but AUC 25% higher and half-life of about 4 hours longer in older women</td>
<td>Dose-normalized trough plasma levels of either venlafaxine or ODV unaltered by age or sex differences. Dosage adjustment based on age or sex is generally not necessary.</td>
<td>Safety and effectiveness in pediatric patients has not been established. No unusual age-associated pattern of adverse events has been observed in elderly patients.</td>
<td>The safety of sertraline has been studied in sample patients aged 6 to 18 years, revealing similar reactions to adults; safety and effectiveness in children younger than age 6 years not established</td>
<td>In a multiple-dose study in the elderly, C\textsubscript{max} is about 70% to 80% greater than the respective C\textsubscript{max} in non-elderly subjects. Initial dosage in elderly patients should be reduced.</td>
<td>Escitalopram AUC and half-life were increased by approximately 50% in elderly subjects, but C\textsubscript{max} was unchanged. 10 mg is the recommended dose for elderly patients.</td>
<td>AUC and half-life were increased in elderly subjects by 30% and 50%, respectively; in a multiple-dose study, they were increased by 23% and 30%, respectively. 20 mg is the recommended dose for most elderly patients.</td>
<td>Data suggest no prominent effect of age on bupropion concentration, but effects of age on the pharmacokinetics of bupropion and its metabolites have not been fully characterized.</td>
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<tr>
<td><strong>Sex</strong></td>
<td>Dosage adjustment based on age is not necessary.</td>
<td>Dosage adjustment based on sex is not necessary.</td>
<td>No information is given in package insert.</td>
<td>Dosage adjustment based on sex is not necessary.</td>
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<td><strong>Liver impairment</strong></td>
<td>Duloxetine should not be administered to patients with any hepatic insufficiency. After a single 20-mg dose in six cirrhotic patients, mean plasma clearance is about 15% of that of age- and sex-matched healthy subjects, with a five-fold increase in mean exposures (AUC).</td>
<td>Elimination half-life prolonged by about 30%; clearance is decreased by about 50% in cirrhotic patients compared with normal subjects. Lower or less frequent dose should be used. Lower or less frequent dose should be used.</td>
<td>Initial dose should be reduced in patients with severe hepatic impairment; upward titration, if necessary, should be at increased intervals. Oral clearance reduced by 37% and half-life doubled in patients with reduced hepatic function compared with normal subjects. 10 mg is the recommended dose for most hepatically impaired patients.</td>
<td>Oral clearance reduced by 37% and half-life doubled in patients with reduced hepatic function compared with normal subjects. 10 mg is the recommended dose for most hepatically impaired patients.</td>
<td>Oral clearance reduced by 37% and half-life doubled in patients with reduced hepatic function compared with normal subjects. 20 mg is the recommended dose for most hepatically impaired patients.</td>
<td>AUCs for bupropion and hydroxybupropion were more variable and tended to be greater (by 53% to 57%) in patients with alcoholic liver disease. Should be used with extreme caution in this population.</td>
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### Special Populations (continued)

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<tr>
<td><strong>Renal impairment</strong></td>
<td>In patients with ESRD or severe renal impairment (CrCl &lt; 30 ml/minute), duloxetine is not recommended.</td>
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<td>Duloxetine C&lt;sub&gt;max&lt;/sub&gt; and AUC values were approximately 100% greater in patients with ESRD receiving chronic intermittent hemodialysis, but elimination half-life was similar to that in normal controls.</td>
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<td>Clinical pharmacology studies have not been conducted in patients with a moderate degree of renal dysfunction, but population pharmacokinetic analyses suggest that mild renal dysfunction has no significant effect on duloxetine’s apparent CrCl.</td>
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<td>Elimination half-life is prolonged by about 50%, and CrCl reduced by about 24% in renally impaired patients compared with normal subjects.</td>
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<td>In dialysis patients, ODV elimination half-life was prolonged by about 142%, and CrCl was reduced by about 56% compared with normal subjects.</td>
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<td>Use of a lower or less frequent dose is not usually necessary in renally impaired patients, but the possibility exists that renally excreted metabolites of fluoxetine might accumulate to higher levels in patients with severe renal dysfunction.</td>
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<td>Multiple-dose pharmacokinetics appear to be unaffected by renal impairment.</td>
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<td></td>
<td>Initial dose should be reduced in patients with severe renal impairment, and upward titration, if necessary, should be at increased intervals.</td>
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<td>In patients with mild-to-moderate renal function impairment, oral clearance is reduced by 17% compared with normal subjects.</td>
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<td>No dose adjustment dosage is recommended for these patients.</td>
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<td></td>
<td>No information is available about patients with severely reduced renal function (CrCl &lt; 20 ml/minute).</td>
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<td>No dose adjustment is recommended for these patients.</td>
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<td>The effect of renal disease on the pharmacokinetics of bupropion has not been studied.</td>
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<td>The elimination of the major metabolites of bupropion may be affected by reduced renal function.</td>
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</tbody>
</table>
### Special Populations (continued)

<table>
<thead>
<tr>
<th>Special Population</th>
<th>Duloxetine HCl</th>
<th>Venlafaxine HCl</th>
<th>Fluoxetine HCl</th>
<th>Sertraline HCl</th>
<th>Paroxetine HCl</th>
<th>Escitalopram oxalate</th>
<th>Citalopram hydrobromide</th>
<th>Bupropion HCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other</td>
<td>Sustained HTN</td>
<td>Sustained HTN</td>
<td>Sustained HTN</td>
<td>Sustained HTN</td>
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<td></td>
<td>In clinical trials, duloxetine was associated with mean increases in BP, averaging 2 mm Hg systolic and 0.5 mm Hg diastolic and an increase in the incidence of at least one measurement of systolic BP over 140 mm Hg compared with placebo.</td>
<td>Dose-related; BP increase between 10 and 15 mm Hg; incidence: • &lt;100 mg/day = 3% • 101–200 mg/day = 5% • 201–300 mg/day = 7% • &gt;300 mg/day = 13%</td>
<td>Sustained HTN 1.7% with 20 mg in an open-label trial of 796 patients</td>
<td>Sustained HTN None</td>
<td>Sustained HTN None</td>
<td>Sustained HTN None</td>
<td>Sustained HTN None</td>
<td>Sustained HTN Increased BP, does not exacerbate ventricular arrhythmias or pulse</td>
</tr>
<tr>
<td>QTc Prolongation</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
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<td>None</td>
<td>None</td>
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<tr>
<td>Laboratory Changes</td>
<td>Laboratory Changes Small mean increases from baseline to endpoint in ALT, AST, CPK, and alkaline phosphatase levels</td>
<td>Increased serum cholesterol (1–2.3 mg/dl); Increased total cholesterol clinically relevant. Duration is dose-dependent.</td>
<td>Laboratory Changes None</td>
<td>Laboratory Changes None</td>
<td>Laboratory Changes None</td>
<td>Laboratory Changes None</td>
<td>Laboratory Changes None</td>
<td>Laboratory Changes None</td>
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<tr>
<td>Smoking Status</td>
<td>Extensive and Poor Metabolizers: Plasma concentrations higher in CYP2D6 poor metabolizers than in extensive metabolizers, but AUCs of venlafaxine and ODV were similar in both metabolizers; thus, no dose adjustment is needed.</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>LV Dysfunction: No apparent effect on pharmacokinetics of bupropion or its metabolites, compared with healthy volunteers. Smoking Status: After a single 150-mg oral dose of bupropion, no statistically significant difference in its ( C_{\text{max}} ) half-life, ( T_{\text{max}} ), AUC, or clearance or its active metabolites in smokers and non-smokers.</td>
</tr>
</tbody>
</table>
Diabetic Peripheral Neuropathic Pain

Raskin et al.13

Raskin et al. performed a 28-week, parallel, multicenter, open-label study to test the safety and tolerability of DLX 60 mg twice daily in treating DPNP.

After the initial screening period, 449 patients were randomly assigned, in a 3:1 ratio, to receive either DLX 60 mg twice daily (n = 334) or DLX 120 mg daily (n = 115). There were no statistical differences in the baseline characteristics of the two groups. The study participants were 52% male and 58% white. Their mean age was 60 years; 94% had type-2 diabetes. The mean duration of neuropathic pain was 3.4 years.

Primary safety outcomes were the rates of ADEs, hypoglycemic events, study discontinuation rates, and changes in vital signs, ECGs, lipid profiles, and glycosylated hemoglobin (HbA1c) levels. Efficacy outcomes included CGI–S and the Brief Pain Inventory (BPI) scores.

The percentage of patients discontinuing treatment early as a result of any cause or lack of efficacy was similar in both treatment groups, but the percentage of patients discontinuing early because of ADEs was higher with DLX 120 mg once daily. Discontinuation rates were higher in the first seven weeks, then declined for the rest of the study.

ADEs that led to discontinuation of therapy included nausea, dizziness, vomiting, fatigue, and somnolence. Except for vomiting and somnolence, the incidence of these limiting ADEs was higher with the 60-mg twice-daily DLX dose.

Mean changes in high-density and low-density lipoprotein-cholesterol and triglycerides were similar in both groups, and changes were statistically, but not clinically, significant. Hypoglycemic episodes and alterations in hepatic enzymes were also not clinically significant. Significant sustained elevated blood pressure affected 5.45% of patients taking DLX twice daily and 5.36% of patients taking DLX once daily.

Mean BPI scores declined by 5.4 points with once-daily DLX and by 5.3 points with twice-daily DLX. Mean CGI–S scores fell by 4.5 points with DLX once daily and by 4.4 points with DLX twice daily. These outcomes were significant, when compared with baseline values; however, the authors did not compare the results between the groups.

The authors concluded that both doses of DLX were safe and well tolerated for patients with DPNP.

Goldstein et al.15

A 12-week, parallel, double-blind, placebo-controlled clinical trial was performed to test the effectiveness of three regimens of DLX in reducing the severity of pain associated with neuropathy.

Participants (n = 457) were assigned to one of four study groups: 115 patients received placebo, 115 received DLX 20 mg daily, 114 received DLX 60 mg daily, and 113 received DLX 60 mg twice daily. There were no statistical differences between treatment or control groups in baseline pain scores or mood assessments. The participants were 61% male and 77% white. Eighty-eight percent had type-2 diabetes for about 11.25 years. The mean duration of neuropathy was 3.8 years.

The primary efficacy endpoint was a change in mean scores of the 24-hour Average Pain Severity (24-hour APS) Scale. Primary endpoints were assessed from diary scores between two visits. Secondary efficacy endpoints included scores from the 24-hour Worst Pain Severity Scale, the 24-hour Night Pain Severity Scale, the Short-Form BPI, the CGI–S Scale, the BDI–II, the Beck Anxiety Inventory (BAI), the Short-Form McGill Pain Questionnaire (MPQ), the Dynamic Allodynia (pain to light touch) Scale, and the average daily intake of acacetaminophen.

Safety endpoints included changes in pulse, blood pressure, and frequency of hypoglycemic events. These endpoints were assessed at baseline and at weeks 1, 2, 3, 4, 6, 8, 10, and 12.

The mean changes in 24-hour APS scores were not significant for the patients receiving DLX 20 mg daily at any time during the 12-week trial. The mean change in 24-hour APS scores was clinically significant every week with DLX 60 mg daily and DLX 60 mg twice daily, compared with placebo (*P < .01 to < .001).

All secondary efficacy parameters were clinically significant for patients taking DLX 60 mg daily and DLX 60 mg twice daily (*P < .01 to < .001). However, only two parameters with DLX 20 mg daily reached statistical significance (changes in mean 24-hour Worst Pain scores and CGI–S scores). The rate of discontinuation attributable to ADEs with DLX 60 mg daily and DLX 60 mg twice daily was statistically significant, compared with placebo.

ADEs experienced by more than 10% of patients receiving DLX 60 mg daily included constipation (14.9%), nausea (16.7%), and somnolence (20.3%). ADEs in patients receiving DLX 60 mg twice daily included constipation (10.6%), decreased appetite (12.4%), dry mouth (15%), dizziness (23%), nausea (27.4%), and somnolence (28.3%).

Thus, DLX 60 mg daily and twice daily were effective for DPNP, and all doses tried were well tolerated.

Fibromyalgia

Arnold et al.18

A 12-week, randomized, multicenter, placebo-controlled, double-blind, parallel-group study was undertaken to assess DLX therapy for FM in patients with or without comorbid MDD.

Baseline characteristics for all patients were statistically similar, but more placebo subjects were naive to antidepressants. After screening, patients entered a one-week placebo lead-in phase to assess baseline characteristics.

The eligible subjects (n = 207) were 89% female and 87% white. The mean age was 49 years, and 38% had MDD. After the lead-in phase, the subjects were assigned to receive either placebo or DLX 60 mg twice daily. The DLX dose was titrated to the study regimen as follows: 20 mg daily for five days, 20 mg twice daily for at least three days, 40 mg twice daily for at least two days, and 60 mg twice daily thereafter, beginning at the fifth weekly visit.

Primary efficacy endpoints were changes in mean pain severity on the FIQ and total FIQ. Secondary efficacy endpoints included changes in mean scores of other areas of the FIQ (fatigue, morning tiredness, and stiffness), the number of tender points, and the mean tender point pain threshold. Other measures included CGI–S, PGI–I, BPI, BDI–II, BAI, Medical Outcomes Study Short Form (SF-36), and SDS scores.

Safety endpoints included ADEs, vital signs, ECGs, and laboratory tests. Patients were assessed every week for two weeks, then every two weeks for the
duration of the trial. FIQ, CGI–S scores, and tender points were assessed on every visit. PGI–I, BPI, BDI–II, BAI, and laboratory assessments were conducted at weeks 4, 8, and 12. Laboratory tests were also assessed on the final visit along with the QLDS, SF-36, and SDS.

For the efficacy endpoints, the patients taking DLX showed greater improvement in FIQ total scores (treatment difference, –5.53; 95% CI, –10.43 to –0.63) \((P = .027)\), compared with subjects receiving placebo (treatment difference, –0.63; 95% CI, –1.45 to –0.19) \((P = .130)\).

The statistically significant differences between the groups included:

- FIQ stiffness subscore \((P = .048)\)
- number of tender points \((P = .002)\)
- mean tender point pain threshold \((P = .002)\)
- CGI–S \((P = .048)\)
- PGI–I \((P = .033)\)
- BPI average pain severity score \((P = .008)\)
- BPI average interference from pain score \((P = .004)\)
- QLDS \((P = .029)\)
- SDS scores \((P = .001)\)

The statistical differences favored DLX over placebo for patients with FM. In the secondary analysis of the FIQ pain scores and BPI scores, DLX accounted for 61.1% and 83.3%, respectively, of the effect of treatment on pain directly, 38.5% and 15.3% of the effect on pain indirectly by improving depressive symptoms, and 0.5% and 1.5% by improving anxiety symptoms. The men did not have a significant response to treatment, although raw data were not reported.

The most common ADEs (insomnia, dry mouth, and constipation) were considered mild to moderate. ADEs were reported by 90.4% of treated subjects and by 74.8% of controls \((P = .003)\). Other ADEs included an increased heart rate \((3.53 \text{ beats/minute} + 11.56 \text{ beats/minute}; P = .005)\), higher blood pressure, and elevated liver enzymes (not significant).

It was concluded that DLX 60 mg orally twice a day was safe and efficacious for treating FM and that the agent’s effects on pain were independent of its effects on depressive symptoms.

Goldenberg et al.\(^{34}\)
These authors published a meta-analy-

Primary efficacy outcomes included changes in the frequency of incontinence episodes (IEFs) and in the Incontinence Quality-of-Life Questionnaire (I-QOL). Other efficacy endpoints included scores from the PGI–I, Patient Global Impression of Severity (PGI–S) Scale, and BDI–II. Primary efficacy endpoints were assessed at every visit, except for the PGI–S (baseline only) and BDI–II (randomization and final visit only). Safety endpoints included monitoring of ADEs, discontinuation of the study, vital signs, and laboratory tests.

There was a significant decrease in IEF for patients using DLX (by seven episodes), compared with controls (by three episodes) \((P < .001)\).

Patients experiencing more than a 50% decrease in IEF included 51.4% of the DLX group and 33.5% of the placebo group \((P < .001)\). Improved I-QOL scores also favored the treated subjects over the controls (by 11 and 6.8 points, respectively) \((P < .001)\). The increase in the duration of the interval between voiding was 20 minutes with DLX and 2 minutes with placebo \((P < .001)\).

Of the patients receiving DLX 40 mg twice daily, 24% reported ADEs that led them to discontinue the trial, compared with 4% of the placebo subjects \((P < .001)\). The most common ADE was mild-to-moderate nausea; 6.4% of patients withdrew because of this effect; 74% of participants who experienced nausea continued the trial until its completion.

The authors concluded that twice-daily DLX 40 mg was safe and effective for women with SUI.

van Kerrebroeck et al.\(^{36}\)
DLX was assessed in women with SUI in a 12-week, multicenter, double-blind, placebo-controlled clinical trial.

Before randomization, the participants completed urinary diaries during a six-week run-in phase consisting of two weeks for screening, two weeks of no drugs, and two weeks of placebo.

The study participants \((n = 494)\) were divided into one of two groups (a control group or a treatment group). Randomization was equal at each site and performed according to 14 or fewer incontinent episodes per week compared with 14 or more episodes weekly to eliminate differences in severity between the groups. The treated patients received

**Stress Urinary Incontinence**

Dmochowski et al.\(^{35}\)
A 12-week, double-blind, multicenter, placebo-controlled trial was designed to evaluate DLX for women with SUI.

One exclusion criterion was the concomitant use of antidepressants. Participants \((n = 683)\) completed a two-week run-in phase (two weeks with no treatment, two weeks with placebo). They were then randomly assigned to one of two groups: controls taking placebo \((n = 339)\) and subjects taking DLX 40 mg twice daily \((n = 344)\). Randomization was equal at each site and was performed based on 14 or fewer episodes versus 14 or more episodes weekly to eliminate differences in severity between the groups. Patients were assessed every two weeks.
DLX 40 mg twice daily. Participants were assessed every four weeks.

The primary efficacy outcome was a change in I–QOL total scores and in IEF. Other efficacy outcomes were PGI–I and the PGI–S scores. All efficacy endpoints were assessed at every visit, except for the PGI–S, which was assessed only at baseline. Safety endpoints were the reporting of ADEs, discontinuation of the trial secondary to ADEs, vital signs, ECG results, and laboratory findings.

Safety was determined by the occurrence of ADEs brought on by treatment, the severity of the ADEs, and discontinuations resulting from these ADEs. Vital signs, ECGs, and laboratory tests were also monitored.

The IEF decreased significantly with treatment: by 50% with DLX and by 29% with placebo (P = .002). However, there was no significant difference in I–QOL scores between DLX usage (5.5 points) and placebo (4.1 points) (P = .127).

Withdrawal from the study attributed to ADEs was statistically greater for the DLX patients (22%) than for those receiving placebo (5%) (P < .001). The most frequent ADE was nausea, which led 5.3% of the study participants to withdraw. Most of the subjects experiencing nausea in the DLX group reported it as mild to moderate and resolving within one week (40%) or within one month (75%). These patients completed the trial.

DLX 40 mg twice daily was therefore regarded as safe and effective for European women with SUI.

Millard et al.37

A 12-week, double-blind, multicenter, placebo-controlled trial was conducted to evaluate the use of DLX in women with SUI. The women (n = 458) ranged from 27 to 79 years of age. They had a history of SUI for three months or more, an IEF of seven or more episodes per week, a history of SUI for three months or more, an IEF of 14 or more episodes weekly) to randomization was stratified by IEF (14 or fewer episodes per week, a two-week placebo free period, and a two-week placebo period), participants were assigned to one of two study groups. Randomization was stratified by IEF (14 or fewer and 14 or more episodes weekly) to equalize severity between the two study groups.

The treatment arm (n = 227) received DLX 40 mg twice daily; the control group (n = 231) received matching placebo twice daily. Baseline characteristics of the patients did not differ statistically.

Primary efficacy outcomes included a mean change in IEF (assessed from patient diary entries) and in I–QOL, PGI–I, and PGI–S scores. All efficacy endpoints were assessed at every visit, except for the PGI–S, which was assessed only at baseline. Safety endpoints were the reporting of ADEs, discontinuation of the trial secondary to ADEs, vital signs, ECG results, and laboratory findings.

Compliance was assessed by a pill count, but nonadherence to the protocol did not lead to discontinuation. The results supported the use of DLX for SUI.

For all subjects, changes in the median IEF with DLX, compared with placebo, were –53.6% and –40%, respectively (P = .05). For more severe cases (an IEF of 14 or more changes), changes were –54.9% and –41.7%, respectively (P = .022).

Changes in mean total I–QOL scores were 10.3 points with DLX and 6.4 points with placebo (P = .007). The DLX arm reported significantly better improvement in all I–QOL subset scores as well: avoidance or limiting behavior (P = .016), psychosocial effects (P = .016), and social embarrassment (P = .005).

ADEs were more prevalent in the treated patients. Discontinuation rates attributed to ADEs were significantly higher in these patients (17.2%) than in those receiving placebo (1.7%) (P < .001).

Nausea was the most common ADE associated with DLX. Most cases were mild to moderate and resolved within one week (60%) to one month (86%). Other ADEs included an increased heart rate (by fewer than three beats/minute); prolonged RR, PR, and QT intervals (not clinically significant); and elevated hepatic enzymes.

The authors concluded that DLX for patients with SUI was safe and effective.

DRUG INTERACTIONS

DLX undergoes hepatic metabolism involving two cytochrome P450 isoenzymes, CYP2D6 and CYP1A2. Drugs that inhibit CYP1A2 (i.e., fluvoxamine maleate [Luvox, Solvay] and some quinolone antibiotics) and CYP2D6 (i.e., paroxetine) isoenzymes result in higher concentrations of DLX. When fluvoxamine (a CYP1A2 inhibitor) was administered with DLX, the area-under-the curve (AUC) concentration was increased by more than five-fold, the Cmax by about 2.5-fold, and the half-life by more than three-fold.2

The AUC concentration, half-life, and Cmax of desipramine (Norpramin, Aventis) were increased by three-fold with tolterodine. This finding suggests that DLX inhibits the metabolism of other drugs metabolized by CYP2D6.

In studies of benzodiazepines such as lorazepam (Ativan, Wyeth) and temazepam (Restoril, Mallinckrodt), the pharmacokinetics of DLX was not affected under steady-state conditions when administered with these agents. Because DLX is highly bound to plasma protein, coadministration of another highly protein-bound drug may increase free concentrations of the other drug, thereby increasing the potential for ADEs.

DOSEAGE AND ADMINISTRATION

For patients with MDD, the recommended dose of DLX is 40 mg/day (given as 20 mg twice a day) up to 60 mg/day (given once daily or 30 mg twice a day) without regard to meals. For patients with DPNP, DLX 60 mg once daily, without regard to meals, is recommended (Table 2).38

DLX is not indicated for patients with end-stage renal disease, severe renal impairment (creatinine clearance below 30 ml/minute), or hepatic impairment. No dosage adjustment is needed for elderly patients.

ADVERSE REACTIONS

The most common ADE of DLX in clinical studies was nausea, which usually subsided within one to two weeks. Other common ADEs are presented in Table 3.

Some people also experienced an increase in blood pressure. For DLX-treated patients, the mean changes in supine systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 1.5 mm Hg, and the mean increase in supine heart rate of 1.5 beats/minute compared with a mean decrease of 0.5 beats/minute in patients taking placebo. DLX did not prolong QTc intervals in patients treated for depression.

No suicides or drug-related deaths were reported during the trials, although suicidal (0.2% for DLX vs. 0.3% for placebo) or self-injurious ideation (0.1% for DLX vs. 0% for placebo) was reported by patients treated for depression.
and benefits. The concomitant use of thioridazine (Mellaril, Novartis) should be avoided because of the potential risk of cardiac arrhythmias.

DLX should not be prescribed for patients with suicidal thoughts. A physician should be notified immediately if any thoughts of suicide are observed.

In clinical trials, DLX was associated with an increased risk of mydriasis, and its use should be avoided in patients with uncontrolled narrow-angle glaucoma.

Both adults and children may experience worsening of depression or the emergence of suicidal ideation and behavior, and they should be observed closely by both families and caregivers for clinical worsening and suicidality, especially at the beginning of the drug therapy or at the time of dose changes.

**COST**

The net wholesale price of DLX is $2.54 per 20-mg capsule and $2.85 per 30- or 60-mg capsule. The average wholesale price is $3.18 per 20-mg capsule and $3.56 per 30- or 60-mg capsule.

**CONCLUSION**

With its ability to inhibit neuronal serotonin and norepinephrine reuptake, DLX has two FDA-approved indications, namely the treatment of major depressive disorder and diabetic peripheral neuropathy. It may have efficacy in the treatment of stress urinary incontinence and fibromyalgia.

DLX 60 mg may be administered once or twice daily. It is associated with high protein binding, changes in blood pressure, and involvement with cytochrome P450 isoenzymes CYP2D6 and CYP1A2.
Common ADEs were nausea, constipation, decreased appetite, dizziness, dry mouth, fatigue, increased sweating, loss of strength or energy, and sleepiness. Blood pressure should be monitored periodically. No suicides or drug-related deaths were reported.

Trials comparing DLX with other antidepressants have either not been designed or have not been adequately powered for such comparisons. In Europe, DLX is prescribed to treat a wide range of emotional and physical symptoms of depression as well as physical symptoms of neuropathy. DLX has not been studied in patients with refractory depression, multiple comorbid disease states, or depression involving chronic pain. Further trials are needed to establish efficacy in the treatment of SUI and FM.

No prospective cost-efficacy studies of DLX therapy for major depressive disorders are available. In the cost-effectiveness trial of DLX 80 mg versus DLX 40 mg versus paroxetine 20 mg/day, as provided in the product dossier, the 80-mg/day dose was less expensive and more effective than paroxetine 20 mg/day. In that study, DLX 40 mg/day was more effective and was less costly than paroxetine, but results were only slightly above expected nondifferentiating values.

REFERENCES