trimester of pregnancy have developed complications that have sometimes been severe and required prolonged hospitalization, respiratory support, enteral nutrition, and other forms of supportive care in special-care nurseries. Such complications can arise immediately upon delivery and usually last several days or up to 2–4 weeks. Clinical findings reported to date in the neonates have included respiratory distress, cyanosis, apnea, seizures, temperature instability or fever, feeding difficulty, dehydration, excessive weight loss, vomiting, hypoglycemia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, reduced or lack of reaction to pain stimuli, and constant crying. These clinical features appear to be consistent with either a direct toxic effect of the SNRI or selective serotonin-reuptake inhibitor or, possibly, a drug withdrawal syndrome. It should be noted that, in some cases, the clinical picture was consistent with serotonin syndrome (see Drug Interactions: Drugs Associated with Serotonin Syndrome, in Fluoxetine Hydrochloride 28:16.04.20). When treating a pregnant woman with duloxetine during the third trimester of pregnancy, the clinician should carefully consider the potential risks and benefits of such therapy. Consideration may be given to cautiously tapering duloxetine therapy in the third trimester prior to delivery if the drug is administered during pregnancy. (See Treatment of Pregnant Women during the Third Trimester under Dosage and Administration: Special Populations.)

Lactation. Duloxetine is distributed into human milk. At steady state, concentrations in breast milk are approximately one-fourth the maternal plasma concentrations. Because the safety of duloxetine in infants is not known, use in nursing women is not recommended. However, if the clinician determines that the potential benefits of duloxetine therapy for the mother outweigh the potential risks to the infant, dosage adjustment is not required since lactation does not affect pharmacokinetics.

Pediatric Use. Safety and efficacy of duloxetine in children younger than 18 years of age have not been established.

FDA warns that a greater risk of suicidal thinking or behavior (suicidality) occurred during first few months of antidepressant treatment (4%) compared with placebo (2%) in children and adolescents with major depressive disorder, obsessive-compulsive disorder (OCD), or other psychiatric disorders based on pooled analyses of 24 short-term, placebo-controlled trials of 9 antidepressant drugs (selective serotonin-reuptake inhibitors [SSRIs] and other antidepressants). However, a more recent meta-analysis of 27 placebo-controlled trials of 9 antidepressants (SSRIs and others) in patients younger than 19 years of age with major depressive disorder, OCD, or non-OCD anxiety disorders suggests that the benefits of antidepressant therapy in treating these conditions may outweigh the risks of suicidal behavior or suicidal ideation. No suicides occurred in these pediatric trials.

Carefully consider these findings when assessing potential benefits and risks of duloxetine in a child or adolescent for any clinical use. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Geriatric Use. Approximately 5.9% of patients studied in major depressive disorder clinical trials and 33% of patients studied in diabetic peripheral neuropathic pain clinical trials of duloxetine were 65 years of age or older. The generalized anxiety disorder clinical trials did not include sufficient numbers of patients 65 years of age or older to determine whether they respond differently than younger adults. Although no overall differences in efficacy or safety were observed between geriatric and younger patients in the major depressive disorder and diabetic peripheral neuropathic pain clinical trials and other clinical experience has not revealed any evidence of age-related differences, the possibility that some older patients may exhibit increased sensitivity to the drug cannot be ruled out.

Clinically important hyponatremia has been reported in geriatric patients. (See Hyponatremia/Syndrome of Inappropriate Antidiuretic Hormone Secretion under Warnings/Precautions: General Precautions, in Cautions.)

In pooled data analyses, a *reduced* risk of suicidality was observed in adults 65 years of age or older with antidepressant therapy compared with placebo. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Hepatic Impairment. Substantially increased exposure to duloxetine; use is not recommended in patients with any hepatic insufficiency or with substantial alcohol use. (See Hepatic Effects under Warnings/Precautions: General Precautions, in Cautions.)

Renal Impairment. Increased plasma concentrations of duloxetine and its metabolites; use is not recommended in patients with end-stage renal disease (requiring dialysis) or severe renal impairment (creatinine clearance less than 30 mL/minute).

Population pharmacokinetic analyses suggest that mild to moderate renal impairment has no clinically important effect on duloxetine apparent clearance.

■ **Common Adverse Effects** Adverse effects reported in 5% or more of patients with major depressive disorder receiving duloxetine and at an incidence at least twice that reported with placebo include nausea, dry mouth, constipation, decreased appetite, fatigue, somnolence, and increased sweating.

Adverse effects reported in 5% or more of patients with generalized anxiety disorder receiving duloxetine and at an incidence at least twice that reported with placebo include nausea, fatigue, dry mouth, somnolence, constipation, insomnia, decreased appetite, vomiting, hyperhidrosis, decreased libido, delayed ejaculation, and erectile dysfunction.

Adverse effects reported in 5% or more of patients with diabetic peripheral neuropathy receiving duloxetine and at an incidence at least twice that reported with placebo include nausea, somnolence, dizziness, dry mouth, constipation, hyperhidrosis, decreased appetite, and asthenia.

Drug Interactions

■ **Drugs Metabolized by Hepatic Microsomal Enzymes** Substrates of cytochrome P-450 (CYP) 2D6 isoenzyme (e.g., tricyclic antidepressants [TCAs; amitriptyline, desipramine, imipramine, nortriptyline], phenothiazines, class IC antiarrhythmics [flecainide, propafenone]): potential pharmacokinetic (increased AUC of the substrate) interactions. Use with caution. Consider monitoring plasma TCA concentrations and reducing the TCA dosage if a TCA is administered concurrently with duloxetine.

Substrates of CYP1A2, CYP3A, CYP2C9, or CYP2C19 isoenzymes: pharmacokinetic interaction is unlikely.

■ **Drugs Affecting Hepatic Microsomal Enzymes** Inhibitors of CYP1A2 (e.g., fluvoxamine, some quinolone anti-infective agents): potential pharmacokinetic (increased plasma duloxetine concentrations) interaction. Avoid concomitant use.

Inhibitors of CYP2D6 (e.g., fluoxetine, paroxetine, quinidine) isoenzymes: potential pharmacokinetic interactions (increased plasma duloxetine concentrations); avoid concomitant use.

■ **Drugs that Affect Gastric Acidity** Theoretical risk of altered duloxetine bioavailability if administered with drugs that increase gastric pH. However, no clinically important effect was demonstrated when duloxetine was administered with aluminum- and magnesium-containing antacids or famotidine.

Whether the concomitant administration of proton-pump inhibitors affects duloxetine absorption is currently unknown.

■ **Protein-bound Drugs** Interactions between duloxetine and highly protein-bound drugs have not been fully evaluated to date. However, duloxetine is highly bound to plasma proteins, and administration of the drug to patients receiving other highly protein-bound drugs may result in increased plasma concentrations of the other drug and increased incidence of adverse effects.

■ **Alcohol** Potential pharmacologic (increased risk of hepatotoxicity) interaction; avoid concomitant use in patients with substantial alcohol use. (See Hepatic Effects under Warnings/Precautions: General Precautions, in Cautions.)

Duloxetine has not been shown to potentiate the impairment of mental and motor skills caused by alcohol.

■ **CNS-active Drugs** Potential pharmacologic interaction with other centrally acting drugs; use with caution.

■ **5-HT$_1$ Receptor Agonists ("Triptans")** Pharmacologic interaction (potentially life-threatening serotonin syndrome) if used concurrently with 5-HT$_1$ receptor agonists (e.g., almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan). If concomitant use is clinically warranted, the patient should be observed carefully, particularly during treatment initiation, when dosage is increased, or when another serotonergic agent is initiated. (See Serotonin Syndrome under Warnings/Precautions: Warnings, in Cautions.)

■ **Monoamine Oxidase Inhibitors** Pharmacologic interaction (potentially fatal serotonin syndrome); concomitant use is contraindicated. The manufacturer recommends that at least 2 weeks should elapse between discontinuance of an MAO inhibitor and initiation of duloxetine and that at least 5 days elapse between discontinuance of duloxetine therapy and initiation of MAO inhibitor therapy. (See Serotonin Syndrome under Warnings/Precautions: Warnings, in Cautions.)

■ **Selective Serotonin-reuptake Inhibitors and Selective Serotonin- and Norepinephrine-reuptake Inhibitors** Potential pharmacologic interaction (potentially life-threatening serotonin syndrome); concurrent administration not recommended. (See Serotonin Syndrome under Warnings/Precautions: Warnings, in Cautions.)

■ **Serotonergic Drugs** Potential pharmacologic interaction (potentially life-threatening serotonin syndrome) with drugs affecting serotonergic neurotransmission, including linezolid (an anti-infective agent that is a nonselective, reversible MAO inhibitor), lithium, tramadol, and St. John's wort *(Hypericum perforatum)*; use with caution. Concurrent administration of serotonin precursors (such as tryptophan) not recommended. (See Serotonin Syndrome under Warnings/Precautions: Warnings, in Cautions.)

■ **Thioridazine** Potential pharmacokinetic (increased plasma thioridazine concentrations) interaction with resulting increased risk of serious ventricular arrhythmias and sudden death; concomitant use is not recommended by manufacturer of duloxetine.

Description

Duloxetine hydrochloride, a selective serotonin- and norepinephrine-reuptake inhibitor (SNRI), is an antidepressant and anxiolytic agent. Duloxetine hydrochloride is pharmacologically related to venlafaxine hydrochloride.

The exact mechanisms of the antidepressant, anxiolytic, and central pain inhibitory actions of duloxetine have not been fully elucidated but appear to be associated with the drug's potentiation of serotonergic and noradrenergic activity in the CNS. Like venlafaxine, duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of do-