ing suicidality. Consequently, consideration should be given to changing the therapeutic regimen or discontinuing therapy in patients whose depression is persistently worse or in patients experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, particularly if such manifestations are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If a decision is made to discontinue therapy, the escitalopram dosage should be tapered as rapidly as is feasible but the risks of abrupt discontinuance should be considered. (See Dosage: Discontinuance of Therapy, in Dosage and Administration.) FDA also recommends that the drugs be prescribed in the smallest quantity consistent with good patient management, in order to reduce the risk of overdosage.

Bipolar Disorder. May unmask bipolar disorder. (See Activation of Mania/Hypomania under Warnings/Precautions: General Precautions, in Cautions.) To screen for patients who may be at risk, obtain a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, depression) prior to initiation of therapy. Escitalopram is *not* approved for use in treating bipolar depression.

General Precautions **Withdrawal of Therapy.** Withdrawal symptoms, including agitation, anxiety, confusion, dizziness, dysphoric mood, emotional lability, headache, hypomania, insomnia, irritability, lethargy, sensory disturbances (e.g., paresthesias such as electric shock sensations), have been reported during the postmarketing surveillance period for escitalopram and other selective serotonin-reuptake inhibitors, particularly upon abrupt discontinuance of these drugs. While these events are generally self-limiting, there have been reports of serious discontinuance symptoms. Therefore, patients should be monitored for these symptoms when discontinuing escitalopram therapy. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. (See Dosage: Discontinuance of Therapy under Dosage and Administration.)

Abnormal Bleeding. Like other psychotropic drugs that interfere with serotonin reuptake, episodes of abnormal bleeding (e.g., upper GI bleeding) have been reported in patients receiving escitalopram. The manufacturer recommends that patients be advised of the risk of bleeding associated with the concomitant use of escitalopram with aspirin or other nonsteroidal anti-inflammatory agents, warfarin, or other drugs that affect coagulation. (See Drug Interactions: Drugs Affecting Hemostasis.)

Syndrome of Inappropriate Antidiuretic Hormone Secretion/Hyponatremia. Like other antidepressants (e.g., citalopram), syndrome of inappropriate antidiuretic hormone (SIADH) secretion or hyponatremia requiring medical intervention and/or escitalopram discontinuance may occur.

Activation of Mania/Hypomania. Activation of mania and hypomania has occurred in patients receiving escitalopram or citalopram. Use with caution in patients with a history of mania. (See Bipolar Disorder under Warnings/Precautions: Warnings, in Cautions.)

Seizures. The risk of seizures associated with escitalopram use has not been systematically evaluated, but seizures have been reported in patients receiving the drug; therefore, as with other antidepressants, initiate with caution in patients with a history of seizures.

CNS Effects. Interference with cognitive and motor performance is possible.

Concomitant Diseases. Experience with escitalopram in patients with concomitant diseases is limited. Patients with recent history of myocardial infarction or unstable heart disease were generally excluded from clinical studies. Use with caution in patients with altered metabolism or hemodynamics.

Specific Populations **Pregnancy.** Category C. (See Users Guide.)

Complications, sometimes severe and requiring prolonged hospitalization, respiratory support, enteral nutrition, and other forms of supportive care, have been reported in some neonates exposed to escitalopram, other SSRIs, or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) late in the third trimester; such complications may arise immediately upon delivery. In addition, an increased risk of persistent pulmonary hypertension of the newborn (PPHN) has been observed in infants exposed to SSRIs during late pregnancy; PPHN is associated with substantial neonatal morbidity and mortality.

Clinicians should carefully consider the potential risks and benefits of escitalopram therapy when used during the third trimester of pregnancy. However, clinicians also should be aware that women who discontinued antidepressant therapy during pregnancy were more likely to experience a relapse of depression than those who remained on antidepressant therapy according to results of one longitudinal study involving women with a history of major depressive disorder who were euthymic while receiving antidepressant therapy at the beginning of pregnancy. Clinicians may consider tapering the dosage of escitalopram in women in the third trimester of pregnancy. (See Pregnancy under Cautions: Pregnancy, Fertility, and Lactation, in Citalopram Hydrobromide 28:16.04.20.)

Lactation. Like racemic citalopram, escitalopram is distributed into human milk. Potential for serious adverse effects (e.g., excessive somnolence, decreased feeding, weight loss) in nursing infants exists. Discontinue nursing or the drug, taking into account the potential risk in nursing infants and the importance of the drug to the mother.

Pediatric Use. Safety and efficacy not established in children younger than 18 years of age. The manufacturer states that escitalopram was not demonstrated to be effective in a placebo-controlled trial in 264 children and adolescents with major depressive disorder.

FDA warns that a greater risk of suicidal thinking or behavior (suicidality) occurred during the 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 escitalopram in a child or adolescent for any clinical use. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Geriatric Use. Experience in those 65 years of age or older insufficient to determine whether they respond differently from younger adults; increased sensitivity cannot be ruled out.

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.)

Renal Impairment. Use with caution in patients with severe renal impairment (i.e., creatinine clearance less than 20 mL/minute). (See Dosage and Administration: Special Populations.)

Hepatic Impairment. In clinical studies, clearance of racemic citalopram was decreased by 37% and elimination half-life was doubled relative to that in patients with normal hepatic function. Dosage reduction recommended for patients with hepatic impairment. (See Dosage and Administration: Special Populations.)

■ **Common Adverse Effects** Adverse effects reported in approximately 5% or more of patients with generalized anxiety or major depressive disorder receiving escitalopram and with an incidence of at least twice that of placebo include insomnia, nausea, increased sweating, sexual dysfunction (ejaculation disorder [primarily ejaculatory delay], decreased libido, anorgasmia), fatigue, and somnolence.

Drug Interactions

■ **Drugs Affecting or Metabolized by Hepatic Microsomal Enzymes** Inhibitors or inducers of cytochrome P-450 (CYP) 3A4 (e.g., carbamazepine, ketoconazole, ritonavir, triazolam) and 2C19 isoenzymes; clinically important pharmacokinetic interaction unlikely since escitalopram is metabolized by multiple enzyme systems. However, possibility that carbamazepine may increase clearance of escitalopram should be considered.

Substrates of cytochrome P-450 (CYP) 2D6 isoenzyme (e.g., desipramine, metoprolol); potential pharmacokinetic (increased peak plasma concentrations and AUC of the substrate) interactions. Use with caution. Increased plasma concentrations of metoprolol have been associated with decreased cardioselectivity.

■ **Drugs Affecting Hemostasis** Pharmacokinetics of warfarin were not affected by racemic citalopram; however, prothrombin time increased by 5%. The effects of escitalopram have not been evaluated, and the clinical importance of this interaction is unknown.

Potential pharmacologic (increased risk of bleeding) interaction with aspirin or other nonsteroidal anti-inflammatory agents, warfarin, or other drugs that affect coagulation; 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 of monoamine oxidase (MAO) inhibitors with escitalopram is contraindicated. In addition, at least 2 weeks should elapse between discontinuance of an MAO inhibitor and initiation of escitalopram and vice versa. (See Serotonin Syndrome under Warnings/Precautions: Warnings, in Cautions.)

Linezolid Pharmacologic interaction (serotonin syndrome) reported; use with caution.

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

■ **Citalopram** Because escitalopram is the more active isomer of racemic citalopram, the 2 agents should not be used concomitantly.

■ **Lithium** Potential pharmacologic interaction (enhanced serotonergic effects of escitalopram and potentially life-threatening serotonin syndrome); use with caution. Pharmacokinetic interaction unlikely.