

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Escitalopram Tablets, USP safely and effectively. See full prescribing information for Escitalopram Tablets, USP.

Escitalopram Tablets, USP

Initial U.S. Approval: 2002

WARNING: Suicidality and Antidepressant Drugs <i>See full prescribing information for complete boxed warning.</i>
Increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders. Escitalopram tablets are not approved for use in pediatric patients less than 12 years of age (5.1).

—RECENT MAJOR CHANGES—

- Warnings and Precautions (5.9) 07/2014

—INDICATIONS AND USAGE—

- Escitalopram is a selective serotonin reuptake inhibitor (SSRI) indicated for:
 - Acute and Maintenance Treatment of Major Depressive Disorder (MDD) in adults and adolescents aged 12-17 years (1.1)
 - Acute Treatment of Generalized Anxiety Disorder (GAD) in adults (1.2)

—DOSAGE AND ADMINISTRATION—

Escitalopram tablets, USP should generally be administered once daily, morning or evening with or without food (2.1, 2.2).

Indication	Recommended Dose
MDD (2.1)	
Adolescents (2.1)	Initial: 10 mg once daily Recommended: 10 mg once daily Maximum: 20 mg once daily
Adults (2.1)	Initial: 10 mg once daily Recommended: 10 mg once daily Maximum: 20 mg once daily
GAD (2.2)	
Adults (2.2)	Initial: 10 mg once daily Recommended: 10 mg once daily

- No additional benefits seen at 20 mg/day dose (2.1).
- 10 mg/day is the recommended dose for most elderly patients and patients with hepatic impairment (2.3).
- No dosage adjustment for patients with mild or moderate renal impairment. Use caution in patients with severe renal impairment (2.3).
- Discontinuing Escitalopram: A gradual dose reduction is recommended (2.4).

—DOSAGE FORMS AND STRENGTHS—

- Tablets: 5 mg, 10 mg (scored) and 20 mg (scored) (3.1)

—CONTRAINDICATIONS—

- Serotonin Syndrome and MAOIs: Do not use MAOIs intended to treat psychiatric disorders with escitalopram or within 14 days of stopping treatment with escitalopram. Do not use escitalopram within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start escitalopram in a patient who is being treated with linezolid or intravenous methylene blue (4.1).
- Pimozide: Do not use concomitantly (4.2).
- Known hypersensitivity to escitalopram or citalopram or any of the inactive ingredients (4.3).

—WARNINGS AND PRECAUTIONS—

- Clinical Worsening/Suicide Risk: Monitor for clinical worsening, suicidality and unusual change in behavior, especially, during the initial few months of therapy or at times of dose changes (5.1).
- Serotonin Syndrome: Serotonin syndrome has been reported with SSRIs and SNRIs, including escitalopram, both when taken alone, but especially when co-administered with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone and St. John's Wort). If such symptoms occur, discontinue escitalopram and initiate supportive treatment. If concomitant use of escitalopram with other serotonergic drugs is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases (5.2).
- Discontinuation of Treatment with Escitalopram: A gradual reduction in dose rather than abrupt cessation is recommended whenever possible (5.3).
- Seizures: Prescribe with care in patients with a history of seizure (5.4).
- Activation of Mania/Hypomania: Use cautiously in patients with a history of mania (5.5).
- Hypotension: Can occur in association with SIAHD (5.6).
- Abnormal Bleeding: Use caution in concomitant use with NSAIDs, aspirin, warfarin or other drugs that affect coagulation (5.7).
- Interference with Cognitive and Motor Performance: Use caution when operating machinery (5.8).
- Angle Closure Glaucoma: Angle closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants (5.9).
- Use in Patients with Concomitant Illness: Use caution in patients with diseases or conditions that produce altered metabolism or hemodynamic responses (5.10).

—ADVERSE REACTIONS—

Most commonly observed adverse reactions (incidence ≥ 5% and at least twice the incidence of placebo patients) are: insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, sweating increased, fatigue and somnolence, decreased libido, and anorgasmia (6.1).

—DRUG INTERACTIONS—

- Concomitant use with SSRIs, SNRIs or Tryptophan: Use cautiously in patients with a history of serotonin syndrome (7.2).
- Use caution when concomitant use with drugs that affect Hemostasis (NSAIDs, Aspirin, Warfarin) (7.6).

—USE IN SPECIFIC POPULATIONS—

- Pregnancy: Use only if the potential benefit justifies the potential risk to the fetus (8.1).
- Nursing Mothers: Caution should be exercised when administered to a nursing woman (8.3)
- Pediatric Use: Safety and effectiveness of escitalopram has not been established in pediatric MDD patients less than 12 years of age (8.4).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

- 12.1 Mechanism of Action
 - 12.2 Pharmacodynamics
 - 12.3 Pharmacokinetics
13. NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
 - 13.2 Animal Toxicology and/or Pharmacology

14. CLINICAL STUDIES

- 14.1 Major Depressive Disorder
- 14.2 Generalized Anxiety Disorder

16. HOW SUPPLIED/STORAGE AND HANDLING

- 16.1 Tablets

17. PATIENT COUNSELING INFORMATION

- 17.1 Information for Patients
- 17.2 FDA-Approved Medication Guide

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNINGS: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of escitalopram or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Escitalopram is not approved for use in pediatric patients less than 12 years of age. (See *Warnings and Precautions: Clinical Worsening and Suicide Risk (5.1)*, *Patient Counseling Information: Information for Patients (17.1)*, and *Use in Specific Populations: Pediatric Use (8.4)*.)

1.1 Major Depressive Disorder

Escitalopram tablets, USP are indicated for the acute and maintenance treatment of major depressive disorder in adults and in adolescents 12 to 17 years of age [see *Clinical Studies (14.1)*]. A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

1.2 Generalized Anxiety Disorder

Escitalopram tablets, USP are indicated for the acute treatment of Generalized Anxiety Disorder (GAD) in adults and adolescents 12 to 17 years of age [see *Clinical Studies (14.2)*]. Generalized Anxiety Disorder (DSM-IV) is characterized by excessive anxiety and worry (apprehensive expectation) that is persistent for at least 6 months and which the person finds difficult to control. It must be associated with at least 3 of the following symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and sleep disturbance.

2. DOSAGE AND ADMINISTRATION

Escitalopram tablets, USP should be administered once daily, in the morning or evening, with or without food.

2.1 Major Depressive Disorder

Initial Treatment

Adolescents

The recommended dose of escitalopram tablets, USP is 10 mg once daily. A flexible-dose trial of escitalopram tablets, USP (10 to 20 mg/day) demonstrated the effectiveness of escitalopram tablets, USP [see *Clinical Studies (14.1)*]. If the dose is increased to 20 mg, this should occur after a minimum of three weeks.

Adults

The recommended dose of escitalopram tablets, USP is 10 mg once daily. A fixed-dose trial of escitalopram tablets, USP demonstrated the effectiveness of escitalopram tablets, USP, but failed to demonstrate a greater benefit of 20 mg over 10 mg [see *Clinical Studies (14.1)*]. If the dose is increased to 20 mg, this should occur after a minimum of one week.

Maintenance Treatment

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacological therapy beyond response to the acute episode. Systematic evaluation of continuing escitalopram tablets, USP 10 or 20 mg/day in adults patients with major depressive disorder who responded while taking escitalopram tablets, USP during an 8-week, acute-treatment phase demonstrated a benefit of such maintenance treatment [see *Clinical Studies (14.1)*]. Nevertheless, the physician who elects to use escitalopram tablets, USP for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient. Patients should be periodically reassessed to determine the need for maintenance treatment.

2.2 Generalized Anxiety Disorder

Initial Treatment

Adults

The recommended starting dose of escitalopram tablets, USP is 10 mg once daily. If the dose is increased to 20 mg, this should occur after a minimum of one week.

Maintenance Treatment

Generalized anxiety disorder is recognized as a chronic condition. The efficacy of escitalopram tablets, USP in the treatment of GAD beyond 8 weeks has not been systematically studied. The physician who elects to use escitalopram tablets, USP for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

2.3 Special Populations

10 mg/day is the recommended dose for most elderly patients and patients with hepatic impairment. No dosage adjustment is necessary for patients with mild or moderate renal impairment. Escitalopram tablets, USP should be used with caution in patients with severe renal impairment.

2.4 Discontinuation of Treatment with Escitalopram Tablets, USP

Symptoms associated with discontinuation of escitalopram tablets, USP and other SSRIs and SNRIs have been reported [see *Warnings and Precautions (5.3)*]. Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

2.5 Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders

At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with escitalopram tablets, USP. Conversely, at least 14 days should be allowed after stopping escitalopram tablets, USP before starting an MAOI intended to treat psychiatric disorders [see *Contraindications (4.1)*].

2.6 Use of Escitalopram Tablets, USP with Other MAOIs such as Linezolid or Methylene Blue (MAOI) Intended to Treat Psychiatric Disorders

Do not start escitalopram tablets, USP in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered [see *Contraindications (4.1)*].

In some cases, a patient already receiving escitalopram tablets, USP therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, escitalopram tablets, USP should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 2 weeks or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with escitalopram tablets, USP may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue [see *Warnings and Precautions (5.2)*].

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1-mg/kg with escitalopram tablets, USP is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use [see *Warnings and Precautions (5.2)*].

2.7 Special Populations

10 mg/day is the recommended dose for most elderly patients and patients with hepatic impairment. No dosage adjustment is necessary for patients with mild or moderate renal impairment. Escitalopram tablets, USP should be used with caution in patients with severe renal impairment.

2.8 Discontinuation of Treatment with Escitalopram Tablets, USP

Symptoms associated with discontinuation of escitalopram tablets, USP and other SSRIs and SNRIs have been reported [see *Warnings and Precautions (5.3)*]. Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

2.9 Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders

At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with escitalopram tablets, USP. Conversely, at least 14 days should be allowed after stopping escitalopram tablets, USP before starting an MAOI intended to treat psychiatric disorders [see *Contraindications (4.1)*].

2.10 Use of Escitalopram Tablets, USP with Other MAOIs such as Linezolid or Methylene Blue (MAOI) Intended to Treat Psychiatric Disorders

Do not start escitalopram tablets, USP in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome. In a patient who requires more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

2.11 Use of Escitalopram Tablets, USP with Other MAOIs such as Linezolid or Methylene Blue (MAOI) Intended to Treat Psychiatric Disorders

Do not start escitalopram tablets, USP in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome [see *Contraindications (4.1)*].

2.12 Use of Escitalopram Tablets, USP with Other MAOIs such as Linezolid or Methylene Blue (MAOI) Intended to Treat Psychiatric Disorders

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2.13 Use of Escitalopram Tablets, USP with Other MAOIs such as Linezolid or Methylene Blue (MAOI) Intended to Treat Psychiatric Disorders

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2.14 Use of Escitalopram Tablets, USP with Other MAOIs such as Linezolid or Methylene Blue (MAOI) Intended to Treat Psychiatric Disorders

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2.15 Use of Escitalopram Tablets, USP with Other MAOIs such as Linezolid or Methylene Blue (MAOI) Intended to Treat Psychiatric Disorders

Do not start escitalopram tablets, USP in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome [see *Contraindications (4.1)*].

2.16 Use of Escitalopram Tablets, USP with Other MAOIs such as Linezolid or Methylene Blue (MAOI) Intended to Treat Psychiatric Disorders

Do not start escitalopram tablets, USP in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome [see *Contraindications (4.1)*].

2.17 Use of Escitalopram Tablets, USP with Other MAOIs such as Linezolid or Methylene Blue (MAOI) Intended to Treat Psychiatric Disorders

Do not start escitalopram tablets, USP in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome [see *Contraindications (4.1)*].

2.18 Use of Escitalopram Tablets, USP with Other MAOIs such as Linezolid or Methylene Blue (MAOI) Intended to Treat Psychiatric Disorders

Do not start escitalopram tablets, USP in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome [see *Contraindications (4.1)*].

2.19 Use of Escitalopram Tablets, USP with Other MAOIs such as Linezolid or Methylene Blue (MAOI) Intended to Treat Psychiatric Disorders

Do not start escitalopram tablets, USP in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome [see *Contraindications (4.1)*].

2.20 Use of Escitalopram Tablets, USP with Other MAOIs such as Linezolid or Methylene Blue (MAOI) Intended to Treat Psychiatric Disorders

Do not start escitalopram tablets, USP in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome [see *Contraindications (4.1)*].

2.21 Use of Escitalopram Tablets, USP with Other MAOIs such as Linezolid or Methylene Blue (MAOI) Intended to Treat Psychiatric Disorders

Do not start escitalopram tablets, USP in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome [see *Contraindications (4.1)*].

2.22 Use of Escitalopram Tablets, USP with Other MAOIs such as Linezolid or Methylene Blue (MAOI) Intended to Treat Psychiatric Disorders

Do not start escitalopram tablets, USP in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome [see *Contraindications (4.1)*].

2.23 Use of Escitalopram Tablets, USP with Other MAOIs such as Linezolid or Methylene Blue (MAOI) Intended to Treat Psychiatric Disorders

Do not start escitalopram tablets, USP in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome [see *Contraindications (4.1)*].

2.24 Use of Escitalopram Tablets, USP with Other MAOIs such as Linezolid or Methylene Blue (MAOI) Intended to Treat Psychiatric Disorders

Do not start escitalopram tablets, USP in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome [see *Contraindications (4.1)*].

2.25 Use of Escitalopram Tablets, USP with Other MAOIs such as Linezolid or Methylene Blue (MAOI) Intended to Treat Psychiatric Disorders

Do not start escitalopram tablets, USP in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome [see *Contraindications (4.1)*].

of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in **Table 1**.

TABLE 1	
Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of treatment, or at times of dose changes, either increases or decreases. The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients receiving antidepressant therapy who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression and/or the emergence of suicidal impulses. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms [see *Dosage and Administration (2.4)*].

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers [see also *Patient Counseling Information (17.1)*]. Prescriptions for escitalopram should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of subsequent manic episodes (i.e., a mood-conversion episode in patients at risk for bipolar disorder). Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder, such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that escitalopram is not approved for use in treating bipolar depression.

5.2 Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including escitalopram, alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort) and with other agents that affect the serotonergic system (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of escitalopram with MAOIs intended to treat psychiatric disorders is contraindicated. Escitalopram should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with escitalopram include information on the route of administration involved: intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. It may be circumstances when it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking escitalopram. Escitalopram should be discontinued before starting treatment with the MAOI [see *Contraindications (4.1)* and *Dosage and Administration (2.5 and 2.6)*].

If concomitant use of escitalopram with other serotonergic drugs including, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases. Treatment with escitalopram and any concomitant serotonergic agents, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

5.3 Discontinuation of Treatment with Escitalopram

During marketing of escitalopram and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been reports of symptoms occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with escitalopram. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate [see *Dosage and Administration (2.4)*].

5.4 Seizures

Although anticonvulsant effects of racemic citalopram have been observed in animal studies, escitalopram has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarketing testing. In clinical trials of escitalopram, cases of convulsion have been reported in association with escitalopram treatment. Like other drugs effective in the treatment of major depressive disorder, escitalopram should be introduced with care in patients with a history of seizure disorder. As with all drugs effective in the treatment of major depressive disorder, escitalopram should be used cautiously in patients with a history of mania.

5.5 Activation of Mania/Hypomania

In placebo-controlled trials of escitalopram in major depressive disorder, activation of mania/hypomania was reported in one (0.1%) of 715 patients treated with escitalopram and in none of the 592 patients with placebo. One patient with a history of hypomania was treated in association with escitalopram treatment. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with racemic citalopram and other marketed drugs effective in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, escitalopram should be used cautiously in patients with a history of mania.

5.6 Hypotension

Faintness or dizziness may occur as a result of treatment with SSRIs and SNRIs, including escitalopram oxalate. In many cases, this hypotension appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), and was reversible when escitalopram was discontinued. Cases with serum sodium lower than 110 mEq/L have been reported. Elderly patients may be at greater risk of developing hypotension with SSRIs and SNRIs. Patients with hypotension or who are otherwise volume depleted may be at greater risk [see *Geriatric Use (8.5)*]. Discontinuation of escitalopram should be considered in patients with symptomatic hypotension and appropriate medical intervention should be instituted.

Signs and symptoms of hypotension include headache, dizziness, concentration, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

5.7 Abnormal Bleeding

SSRIs and SNRIs, including escitalopram, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants may add to the risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with platelet aggregation and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of escitalopram and NSAIDs, aspirin, or other drugs that affect coagulation.

5.8 Interference with Cognitive and Motor Performance

In a study in normal volunteers, escitalopram 10 mg/day did not produce impairment of intellectual function or psychomotor performance. Because any psychoactive drug may impair judgment, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that escitalopram therapy does not affect their ability to engage in such activities.

5.9 Angle Closure Glaucoma

Angle-Closure Glaucoma: The pupillary dilation that occurs following use of many antidepressant drugs including

- Are taking certain drugs such as:
 - Triptans used to treat migraine headache
 - Medicines used to treat mood, anxiety, psychotic or thought disorders, including tricyclics, lithium, SSRIs, SNRIs, or antipsychotics
 - tramadol
- Over-the-counter supplements such as tryptophan or St. John's Wort
- have liver problems
- have kidney problems
- have heart problems
- have or had seizures or convulsions
- have bipolar disorder or mania
- have low sodium levels in your blood
- have a history of a stroke
- have high blood pressure
- have or had bleeding problems

- are pregnant or plan to become pregnant. It is not known if escitalopram will harm your unborn baby. Talk to your healthcare provider about the benefits and risks of treating depression during pregnancy
- are breast-feeding or plan to breast-feed. Some escitalopram may pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby while taking escitalopram.

Tell your healthcare provider about all the medicines that you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Escitalopram and some medicines may interact with each other, may not work as well, or may cause serious side effects.

Your healthcare provider or pharmacist can tell you if it is safe to take escitalopram with your other medicines. Do not start or stop any medicine while taking escitalopram without talking to your healthcare provider first.

If you take escitalopram, you should not take any other medicines that contain escitalopram oxalate or citalopram hydrobromide including: Celexa.

How should I take escitalopram?

- Take escitalopram exactly as prescribed. Your healthcare provider may need to change the dose of escitalopram until it is the right dose for you.
- Escitalopram may be taken with or without food.
- If you miss a dose of escitalopram, take the missed dose as soon as you remember. If it is almost time for the next dose, skip the missed dose and take your next dose at the regular time. Do not take two doses of escitalopram at the same time.
- If you take too much escitalopram, call your healthcare provider or poison control center right away, or get emergency treatment.

What should I avoid while taking escitalopram?

Escitalopram can cause sleepiness or may affect your ability to make decisions, think clearly, or react quickly. You should not drive, operate heavy machinery, or do other dangerous activities until you know how escitalopram affects you. Do not drink alcohol while using escitalopram.

What are the possible side effects of escitalopram?

Escitalopram may cause serious side effects, including all of those described in the section entitled "What is the most important information I should know about escitalopram?"

Common possible side effects in people who take escitalopram include:

- Nausea
- Sleepiness
- Weakness
- Dizziness
- Feeling anxious
- Trouble sleeping
- Sexual problems
- Sweating
- Shaking
- Not feeling hungry
- Dry mouth
- Constipation
- Infection
- Yawning

Other side effects in children and adolescents include:

- increased thirst
- abnormal increase in muscle movement or agitation
- nose bleed
- difficult urination
- heavy menstrual periods
- possible slowed growth rate and weight change. Your child's height and weight should be monitored during treatment with escitalopram.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of escitalopram.

For more information, ask your healthcare provider or pharmacist.

CALL YOUR DOCTOR FOR MEDICAL ADVICE ABOUT SIDE EFFECTS. YOU MAY REPORT SIDE EFFECTS TO THE FDA AT 1-800-FDA-1088.

How should I store escitalopram tablets?

- Store at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F) [See USP Controlled Room Temperature].
- Keep escitalopram tablets bottle closed tightly.

Keep escitalopram and all medicines out of the reach of children.

General information about escitalopram

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use escitalopram for a condition for which it was not prescribed. Do not give escitalopram to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about escitalopram. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider or pharmacist for information about escitalopram that is written for healthcare professionals.

For more information, call toll-free 1-800-313-4623.

What are the ingredients in escitalopram tablets?

Active ingredient: escitalopram oxalate USP

Inactive ingredients: talc, croscarmellose sodium, microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate. The film coating contains hypromellose, titanium dioxide, and polyethylene glycol.

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R. Only

Manufactured by: Jubilant Generics Limited Roorkee - 247661, India

Marketed by: Jubilant Cadista Pharmaceuticals Inc. Salisbury, MD 21801, USA

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

Somnolence	1%	4%	9%
Dizziness	2%	4%	7%
Sweating/Increased	<1%	3%	8%
Constipation	1%	3%	6%
Fatigue	2%	2%	6%
Indigestion	1%	2%	6%

Male and Female Sexual Dysfunction with SSRIs

Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence.

	TABLE 5		
	Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials		
Adverse Event	Escitalopram	Placebo	
	(N=407)	(N=383)	In Males Only
Ejaculation Disorder (primarily ejaculatory delay)	12%	1%	
Libido Decreased	6%	2%	
Impotence	2%	<1%	
	In Females Only		
	(N=737)	(N=636)	
Libido Decreased	3%	1%	
Anorgasmia	3%	<1%	

There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Priapism has been reported with all SSRIs.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Vital Sign Changes

Escitalopram and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with escitalopram treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving escitalopram indicated that escitalopram treatment is not associated with orthostatic changes.

Weight Changes

Patients treated with escitalopram in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight.

Laboratory Changes

Escitalopram and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with escitalopram treatment.

ECG Changes

Electrocardiograms from escitalopram (N=625) and placebo (N=527) groups were compared with respect to outliers defined as subjects with QTc changes over 60 msec from baseline or absolute values over 500 msec post-dose, and subjects with heart rate increases to over 100 bpm or decreases to less than 50 bpm with a 25% change from baseline (bradycardic or bradycardic outliers, respectively). None of the patients in the escitalopram group had a QTc interval >50 msec or a prolongation >40 msec compared to 0.2% of patients in the placebo group. The incidence of tachycardic outliers was 0.2% in the escitalopram and the placebo group.The incidence of bradycardic outliers was 0.5% in the escitalopram group and 0.2% in the placebo group.

QTc interval was evaluated in a randomized, placebo and active (moxifloxacin 400 mg) controlld crossover study, escalating multiple-dose study in 113 healthy subjects. The maximum mean (95% upper confidence bound) difference from placebo arm were 4.5 (6.4) and 10.7 (12.7) msec for 20 mg and supratherapeutic 30 mg escitalopram given once daily, respectively. Based on the established exposure-response relationship, the predicted QTc change from placebo arm (95% confidence interval) under the C_{max} for the dose of 20 mg is 6.6 (7.9) msec. For escitalopram 30 mg given once daily resulted in mean C_{max} of 1.7-fold higher than the mean C_{max} for the maximum recommended therapeutic dose at steady state (20 mg). The exposure under supratherapeutic 30 mg dose is similar to the steady state concentrations expected in CYP2C19 poor metabolizers following a therapeutic dose of 20 mg.

Other Reactions Observed During the Premarketing Evaluation of Escitalopram

Following is a list of treatment-emergent adverse events, as defined in the introduction to the **ADVERSE REACTIONS** section, reported by the 1428 patients treated with escitalopram for periods of up to one year in double-blind or long-term studies. The maximum mean (95% upper confidence bound) difference between events already listed in **Tables 2 & 3**, those events for which a drug cause was remote and at a rate less than 1% or lower than placebo, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acute life threatening. Events are categorized by body system. Events of major clinical importance are described in the Warnings and Precautions section (5).

Cardiovascular - hypertension, palpitation.

Central and Peripheral Nervous System Disorders - light-headed feeling, migraine.

Gastrointestinal Disorders - abdominal cramp, heartburn, gastroenteritis.

General - allergy, chest pain, fever, hot flashes, pain in limb.

Metabolic and Nutritional Disorders - increased weight.

Musculoskeletal System Disorders - arthralgia, myalgia jaw stiffness.

Psychiatric Disorders - appetite increased, concentration impaired, irritability.

Reproductive Disorders-Female - menstrual cramps, menstrual disorder.

Respiratory System Disorders - bronchitis, coughing, nasal congestion, sinus congestion, sinus headache.

Skin and Appendages Disorders - rash.

Special Senses - vision blurred, tinted.

Urinary System Disorders - urinary frequency, urinary tract infection.

The following additional adverse reactions have been identified from spontaneous reports of escitalopram reported worldwide. These adverse reactions have been chosen for inclusion because of a combination of factors, including frequent reporting, or potential similarity to escitalopram and have not been listed elsewhere in labeling. However, because these adverse reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events include:

Blood and Lymphatic System Disorders: anemia, agranulocytis, aplastic anemia, hemolytic anemia, idiopathic thrombocytopenia purpura, leukopenia, thrombocytopenia.

Cardio Disorders: chest tightness, bradycardia, cardiac failure, myocardial infarction, tachycardia, torsade de pointes, ventricular arrhythmia, ventricular tachycardia.

Ear and labyrinth disorders: vertigo

Endocrine Disorders: diabetes mellitus, hyperprolactinemia, SIADH.

Eye Disorders: angle closure glaucoma, diplopia, mydriasis, visual disturbance.

Gastrointestinal Disorder: dysphagia, gastrointestinal hemorrhage, gastroesophageal reflux, pancreatitis, rectal hemorrhage.

General Disorders and Administration Site Conditions: abnormal gal, asthenia, edema, fall, feeling abnormal, malaise.

Hepatobiliary Disorders: fulminant hepatitis, hepatic failure, hepatic necrosis, hepatitis.

Immune System Disorders: allergic reaction, anaphylaxis.

Investigations: bilirubin increased, decreased weight, electrocardiogram QT prolongation, hepatic enzymes increased, hypercholesterolemia, INR increased, prothrombin decreased.

Metabolism and Nutrition Disorders: hyperglycemia, hypoglycemia, hypokalemia, hyponatremia.

Musculoskeletal and Connective Tissue Disorders: muscle cramp, muscle stiffness, muscle weakness, myalgia, osteoarthritis.

Nervous System Disorders: akathisia, amnesia, ataxia, choreoathetosis, cerebrovascular accident, dysarthria, dyskinesia, dystonia, extrapyramidal disorders, grand mal seizures (or convulsions), hypoaesthesia, myoclonus, nystagmus, Parkinsonism, restless legs, suture, syncope, tardive dyskinesia, tremor.

Pregnancy, Puerperium and Perinatal Conditions: spontaneous abortion.

Psychiatric Disorders: acute psychosis, aggression, agitation, anger, anxiety, apathy, completed suicide, confusion, depersonalization, depression aggravated, delirium, delusion, disorientation, feeling unreal, hallucinations (visual and auditory), mood swings, nervousness, nightmare, panic reaction, paranoia, restlessness, self-harm or thoughts of self-harm, suicide attempt, suicidal ideation, suicidal tendency.

Renal and Urinary Disorders: acute renal failure, dysuria, urinary retention.

Reproductive System and Breast Disorders: menorrhagia, priapism.

Respiratory, Thoracic and Mediastinal Disorders: dyspnea, epistaxis, pulmonary embolism, pulmonary hypertension of the newborn.

Skin and Subcutaneous Tissue Disorders: alopecia, angioedema, dermatitis, ecchymosis, erythema multiforme, photosensitivity reaction.

Stevens Johnson Syndrome, toxic epidermal necrolysis, urticaria.

Vascular Disorders: deep vein thrombosis, flushing, hypertensive crisis, hypotension, orthostatic hypotension, phlebitis, thrombosis.

7 DRUG INTERACTIONS

7.1 Monoamine Oxidase Inhibitors (MAOIs)
[See Dosage and Administration (2.5 and 2.6), Contraindications (4.1) and Warnings and Precautions (5.2)].

7.2 Serotonergic Drugs
[See Dosage and Administration (2.5 and 2.6), Contraindications (4.1) and Warnings and Precautions (5.2)].

7.3 Triptans

There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of escitalopram with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases [see *Warnings and Precautions* (5.2)].

7.4 CNS Drugs

Given the primary CNS effects of escitalopram, caution should be used when it is taken in combination with other centrally acting drugs.

7.5 Alcohol

Although escitalopram did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications, the use of alcohol by patients taking escitalopram is not recommended.

7.6 Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.)

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate the risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when escitalopram is initiated or discontinued.

7.7 Cimetidine

In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of 400 mg twice a day cimetidine for 8 days resulted in an increase in citalopram AUC and C_{max} of 43% and 39%, respectively. The clinical significance of these findings is unknown.

7.8 Digoxin

In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of citalopram and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin.

7.9 Lithium

Coadministration of racemic citalopram (40 mg/day for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. Nevertheless, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of escitalopram, caution should be exercised when escitalopram and lithium are coadministered.

7.10 Pimozide and Celexa

In a controlled study, a single dose of pimozide 2 mg co-administered with racemic citalopram 40 mg given once daily for 11 days was associated with a mean increase in QTc values of approximately 10 msec compared to pimozide given alone. Racemic citalopram did not alter the mean AUC or C_{max} of pimozide. The mechanism of this pharmacodynamic interaction is not known.

7.11 Sumatriptan

There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and/or an SSRI (e.g., fluoxetine, paroxetine, sertraline, citalopram, escitalopram) is clinically warranted, appropriate observation of the patient is advised.

7.12 Theophylline

Combined administration of racemic citalopram (40 mg/day for 21 days) and the CYP1A2 substrate theophylline (single dose of 300 mg) did not affect the pharmacokinetics of theophylline. The effect of theophylline on the pharmacokinetics of citalopram was not evaluated.

7.13 Warfarin

Administration of 40 mg/day racemic citalopram for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown.

7.14 Carbamazepine

Combined administration of racemic citalopram (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not significantly affect the pharmacokinetics of carbamazepine, a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme-inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of escitalopram should be considered if the two drugs are coadministered.

7.15 Triazolam

Combined administration of racemic citalopram (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either citalopram or triazolam.

7.16 Ketoconazole

Combined administration of racemic citalopram (40 mg) and ketoconazole (200 mg), a potent CYP3A4 inhibitor, decreased the C_{max} and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram.

7.17 Ritonavir

Combined administration of a single dose of ritonavir (600 mg), both a CYP3A4 substrate and a potent inhibitor of CYP3A4, and escitalopram (20 mg) did not affect the pharmacokinetics of either ritonavir or escitalopram.

7.18 CYP3A4 and -2C19 Inhibitors

In vitro studies indicated that CYP3A4 and -2C19 are the primary enzymes involved in the metabolism of escitalopram. However, coadministration of escitalopram (20 mg) and ritonavir (600 mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of escitalopram. Because escitalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease escitalopram clearance.

7.19 Drugs Metabolized by Cytochrome P4502D6

In vitro studies did not reveal an inhibitory effect of escitalopram on CYP2D6. In addition, steady state levels of racemic citalopram were different in poor metabolizers and an odverse CYP2D6 metabolizers after multiple-dose administration of citalopram, suggesting that coadministration, with escitalopram, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on escitalopram metabolism. However, there are limited *in vivo* data suggesting a modest CYP2D6 inhibitory effect for escitalopram. I.e., coadministration of escitalopram (20 mg/day for 21 days) with the tricyclic antidepressant desipramine (single dose of 50 mg), a substrate for CYP2D6, resulted in a 40% increase in C_{max} and a 100% increase in AUC of desipramine. The clinical significance of this finding is unknown. Nevertheless, caution is indicated in the coadministration of escitalopram and drugs metabolized by CYP2D6.

7.20 Metoprolol

Administration of 20 mg/day escitalopram for 21 days in healthy volunteers resulted in a 50% increase in C_{max} and 82% increase in AUC of the beta₁-adrenergic blocker metoprolol given in a single dose of 100 mg). Increased metoprolol plasma levels have been associated with decreased cardiac electivity. Coadministration of escitalopram and metoprolol had no clinically significant effects on blood pressure or heart rate.

7.21 Electroconvulsive Therapy (ECT)

There are no clinical studies of the combined use of ECT and escitalopram.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

In a rat embryofetal development study, oral administration of escitalopram (56, 112, or 150 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased fetal body weight and associated delays in ossification at the two higher doses (approximately 56 times the maximum recommended human dose [MRHD]) of 20 mg/day on a body surface area (mg/m² basis). Maternal toxicity (clinical signs and decreased body weight gain and food consumption), mild to 56 mg/kg/day, was present at all dose levels. The development of fetuses at the highest dose (150 mg/kg/day) was approximately 28 times the MRHD on a mg/m² basis. No teratogenicity was observed at any of the doses tested (as high as 75 times the MRHD on a mg/m² basis).

When female rats were treated with escitalopram (6, 12, 24, or 48 mg/kg/day) during pregnancy and through weaning, slightly increased offspring mortality and growth retardation were noted at 48 mg/kg/day which is approximately 24 times the MRHD on a mg/m² basis. Slight maternal toxicity (clinical signs and decreased body weight gain and food consumption) was seen at this dose. Slightly increased offspring mortality was also seen at 24 mg/kg/day. The no-effect dose was 12 mg/kg/day which is approximately 6 times the MRHD on a mg/m² basis.

In an animal reproduction studies, racemic citalopram has been shown to have adverse effects on embryofetal and postnatal development, including teratogenic effects, when administered at doses greater than human therapeutic doses.

In two rat embryofetal development studies, oral administration of racemic citalopram (32, 56, or 112 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased embryofetal growth and survival and an increased incidence of fetal abnormalities (including cardiovascular and skeletal defects) at the high dose. This dose was also associated with maternal toxicity (clinical signs and decreased body weight gain). The developmental no-effect dose was 56 mg/kg/day. In a rabbit study, no adverse effects on embryofetal development were observed at doses of racemic citalopram of up to 16 mg/kg/day. Thus, teratogenic effects of racemic citalopram were observed at a maternally toxic dose in the rat and were not observed in the rabbit.

When female rats were treated with racemic citalopram (4.8, 12.8, or 32 mg/kg/day) from late gestation through weaning, increased offspring mortality during the first 4 days after birth and persistent offspring growth retardation were observed at the highest dose. The no-effect dose was 12.8 mg/kg/day. Similar effects on offspring mortality and growth were seen when dams were treated throughout gestation and early lactation at doses ≥ 24 mg/kg/day. This dose was also associated with maternal toxicity (clinical signs and decreased body weight gain). The no-effect dose was not determined in that study.

There are no adequate and well-controlled studies in pregnant women. Therefore, escitalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy-Nonteratogenic Effects

Neonates exposed to escitalopram and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotension, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [see *Warnings and Precautions* (5.2)].

Infants exposed to SSRIs in pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 - 2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. Several recent epidemiologic studies suggest a positive statistical association between SSRI use (including escitalopram) in pregnancy and PPHN. Other studies do not show a significant statistical association.

Physicians should also note the results of a prospective longitudinal study of 201 pregnant women with a history of major depression, who were either on antidepressants or had received antidepressants less than 12 weeks prior to their last menstrual period, and were in remission. Women who discontinued antidepressant medication during pregnancy showed a significant increase in relapse of their major depression compared to those women who remained on antidepressant medication throughout pregnancy. When treating a pregnant woman with escitalopram, the physician should carefully consider both the potential risks of taking an SSRI, along with the established benefits of treating depression with an antidepressant. This decision can only be made on a case by case basis [see Dosage and Administration (2.1)].

8.2 Labor and Delivery

The effect of escitalopram on labor and delivery in humans is unknown.

8.3 Nursing Mothers