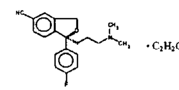
DESCRIPTION

Escitalopram oxalate is an orally administered selective serotonin reuptake inhibitor (SSRI). Escitalopram is the pure S-enantiomer (single isomer) of the racemic bicyclic phthalane derivative citalopram. Escitalopram oxalate is designated S-(+)-1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile oxalate with the following structural formula



The molecular formula is $C_{20}H_{21}FN_2O \cdot C_2H_2O_4$ and the molecular weight is 414 40

Escitalopram oxalate occurs as a fine white to slightly yellow powder and is freely soluble in methanol and dimethyl sulfoxide (DMSO) soluble in isotonic saline solution sparingly soluble in water and ethanol slightly soluble in ethyl acetate and insoluble in heptane

Escitalopram oxalate 10 mg capsules have a grey body and dark grey cap and contain escitalopram oxalate equivalent to 10 mg escitalopram base Escitalopram oxalate 20 mg capsules have an ivory body and brown cap and contain escitalopram oxalate equivalent to 20 mg escitalopram base The capsules also contain the following inactive ingredients croscarmellose sodium edible inks gelatin magnesium stearate microcrystalline cellulose silicon dioxide colloidal talc and titanium dioxide The following coloring agents are used in the 10 mg (dark grey) capsules black iron oxide The following coloring agents are used in the 20 mg (brown) capsules red iron oxide and yellow iron oxide

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of antidepressant action of escitalopram the S-enantiomer of racemic citalopram, is presumed to be linked to potentiation of serotonergic activity in the central nervous system (CNS) resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT) *In vitro* and *in vivo* studies in animals suggest that escitalopram is a highly selective serotonin reuptake inhibitor (SSRI) with minimal effects on norepinephrine and dopamine neuronal reuptake Escitalopram is at least 100-fold more potent than the R-enantiomer with respect to inhibition of 5-HT reuptake and inhibition of 5-HT neuronal firing rate Tolerance to a model of antidepressant effect in rats was not induced by long-term (up to 5 weeks) treatment with escitalopram. Escitalopram has no or very low affinity for serotonergic ($5\text{-}HT_{1-7}$) or other receptors including alpha- and beta adrenergic dopamine (D_{1-5}) histamine (H_{1-3}) muscarinic (M_{1-5}) and benzodiazepine receptors Escitalopram also does not bind to or has low affinity for various ion channels including Na^+ K^+ Cl^- and Ca^{++} channels Antagonism of muscarinic histaminergic and adrenergic receptors has been hypothesized to be associated with various anticholinergic sedative and cardiovascular side effects of other psychotropic drugs

Pharmacokinetics

The single and multiple dose pharmacokinetics of escitalopram are linear and dose-proportional in a dose range of 10 to 30 mg/day Biotransformation of escitalopram is mainly hepatic with a mean terminal half-life of about 27 to 32 hours With once-daily dosing, steady state plasma concentrations are achieved within approximately one week. At steady state the extent of accumulation of escitalopram in plasma in young healthy subjects was 2 2 to 2 5 times the plasma concentrations observed after a single dose The tablet and the oral solution dosage forms of escitalopram oxalate are bioequivalent

Absorption and Distribution

Following a single oral dose (20 mg tablet or solution) of escitalopram, peak blood levels occur at about 5 hours Absorption of escitalopram is not affected by food

The absolute bioavailability of citalopram is about 80% relative to an intravenous dose and the volume of distribution of citalopram is about 12 L/kg Data specific on escitalopram are unavailable

The binding of escitalopram to human plasma proteins is approximately 56%

Metabolism and Elimination

Following oral administrations of escitalopram the fraction of drug recovered in the urine as escitalopram and S demethylcitalopram (S-DCT) is about 8% and 10% respectively The oral clearance of escitalopram is 600 mL/min with approximately 7% of that due to renal clearance

Escitalopram is metabolized to S DCT and S-didemethylcitalopram (S DDCT) In humans unchanged escitalopram is the predominant compound in plasma. At steady state the concentration of the escitalopram metabolite S DCT in plasma is approximately one-third that of escitalopram The level of S-DDCT was not detectable in most subjects *In vitro* studies show that escitalopram is at least 7 and 27 times more potent than S DCT and S DDCT respectively in the inhibition of serotonin reuptake suggesting that the metabolites of escitalopram do not contribute significantly to the antidepressant actions of escitalopram. S-DCT and S DDCT also have no or very low affinity for serotonergic ($5\text{-}HT_{1-7}$) or other receptors including alpha and beta adrenergic dopamine (D_{1-5}) histamine (H_{1-3}) muscarinic (M_{1-5}) and benzodiazepine receptors S-DCT and S DDCT also do not bind to various ion channels including Na^+ K^+ Cl^- and Ca^{++} channels

In vitro studies using human liver microsomes indicated that CYP3A4 and CYP2C19 are the primary isozymes involved in the N demethylation of escitalopram.

Population Subgroups

Age Escitalopram pharmacokinetics in subjects ≥ 65 years of age were compared to younger subjects in a single dose and a multiple-dose study Escitalopram AUC and half life were increased by approximately 50% in elderly subjects and C_{max} was unchanged 10 mg is the recommended dose for elderly patients (see **DOSAGE AND ADMINISTRATION**)

Gender In a multiple-dose study of escitalopram (10 mg/day for 3 weeks) in 18 male (9 elderly and 9 young) and 18 female (9 elderly and 9 young) subjects there were no differences in AUC C_{max} and half-life between the male and female subjects No adjustment of dosage on the basis of gender is needed

Reduced hepatic function Citalopram oral clearance was reduced by 37% and half life was doubled in patients with reduced hepatic function compared to normal subjects 10 mg is the recommended dose of escitalopram for most hepatically impaired patients (see **DOSAGE AND ADMINISTRATION**)

Reduced renal function In patients with mild to moderate renal function impairment oral clearance of citalopram was reduced by 17% compared to normal subjects No adjustment of dosage for such patients is recommended No information is available about the pharmacokinetics of escitalopram in patients with severely reduced renal function (creatinine clearance < 20 mL/min)

Drug-Drug Interactions

In vitro enzyme inhibition data did not reveal an inhibitory effect of escitalopram on CYP3A4 1A2 2C9 2C19 and 2E1 Based on *in vitro* data, escitalopram would be expected to have little inhibitory effect on *in vivo* metabolism mediated by these cytochromes While *in vivo* data to address this question are limited results from drug interaction studies suggest that escitalopram, at a dose of 20 mg has no 3A4 inhibitory effect and a modest 2D6 inhibitory effect. See **Drug Interactions** under **PRECAUTIONS** for more detailed information on available drug interaction data.

Clinical Efficacy Trials

Major Depressive Disorder

The efficacy of escitalopram as a treatment for major depressive disorder was established in three 8-week, placebo-controlled studies conducted in outpatients between 18 and 65 years of age who met DSM IV criteria for major depressive disorder The primary outcome in all three studies was change from baseline to endpoint in the Montgomery Asberg Depression Rating Scale (MADRS)

A fixed-dose study compared 10 mg/day escitalopram and 20 mg/day escitalopram to placebo and 40 mg/day citalopram. The 10 mg/day and 20 mg/day escitalopram treatment groups showed significantly greater mean improvement compared to placebo on the MADRS The 10 mg and 20 mg escitalopram groups were similar on this outcome measure

In a second fixed-dose study of 10 mg/day escitalopram and placebo the 10 mg/day escitalopram treatment group showed significantly greater mean improvement compared to placebo on the MADRS

In a flexible-dose study comparing escitalopram, titrated between 10 and 20 mg/day to placebo and citalopram titrated between 20 and 40 mg/day the escitalopram treatment group showed significantly greater mean improvement compared to placebo on the MADRS

Analyses of the relationship between treatment outcome and age gender and race did not suggest any differential responsiveness on the basis of these patient characteristics

INDICATIONS AND USAGE

Major Depressive Disorder

Escitalopram is indicated for the treatment of major depressive disorder

The efficacy of escitalopram in the treatment of major depressive disorder was established in three 8 week placebo-controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-IV category of major depressive disorder (see **CLINICAL PHARMACOLOGY**)

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

The efficacy of escitalopram in hospitalized patients with major depressive disorders has not been adequately studied. The physician who elects to use escitalopram for extended periods should periodically re-evaluate the long term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**)

CONTRAINDICATIONS

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see **WARNINGS**

Escitalopram is contraindicated in patients with a hypersensitivity to escitalopram or citalopram or any of the inactive ingredients in escitalopram oxalate capsules

In patients receiving serotonin [illegible] e inhibitor drugs in combination with a monoamine oxidase inhibitor (MAOI) there have been rep[illegible] enous, sometimes fatal reactions including hyperthermia, rigidity, myoclonus, autonomic instability [illegible] possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome Furthermore limited animal data on the effects of combined use of SSRIs and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that escitalopram should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping escitalopram before starting an MAOI.

Serotonin syndrome has been reported in two patients who were concomitantly receiving linezolid, an antibiotic which is a reversible non selective MAOI

Clinical Worsening and Suicide Risk

Patients with major depressive disorder both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) whether or not they are taking antidepressant medications and this risk may persist until significant remission occurs Although there has been a long standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients a causal role for antidepressants in inducing such behaviors has not been established **Nevertheless, patients being treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases.** Consideration should be given to changing the therapeutic regimen including possibly discontinuing the medication in patients whose depression is persistently worse or whose emergent suicidality is severe abrupt in onset or was not part of the patient's presenting symptoms

Because of the possibility of co morbidity between major depressive disorder and other psychiatric and nonpsychiatric disorders the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and nonpsychiatric disorders

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 either the worsening of depression and/or the emergence of suicidal impulses has not been established consideration should be given to changing the therapeutic regimen including possibly discontinuing the medication in patients for whom such symptoms are severe abrupt in onset or were not part of the patient's presenting symptoms

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, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Prescriptions for escitalopram should be written for the smallest quantity of capsules consistent with good patient management in order to reduce the risk of overdose

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 **PRECAUTIONS and DOSAGE AND ADMINISTRATION Discontinuation of Treatment with Escitalopram** for a description of the risks of discontinuation of escitalopram)

It should be noted that escitalopram is not approved for use in treating any indications in the pediatric population

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 precipitation of a mixed/manic 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 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

PRECAUTIONS

General

Discontinuation of Treatment with Escitalopram

During marketing of escitalopram and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors) there have been spontaneous reports of adverse events 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**)

Abnormal Bleeding

Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake Subsequent epidemiological studies both of the case control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding In two studies concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (see **Drug Interactions**) Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of escitalopram with NSAIDs aspirin or other drugs that affect coagulation

Hyponatremia

One case of hyponatremia has been reported in association with escitalopram treatment Several cases of hyponatremia or SIADH (syndrome of inappropriate antidiuretic hormone secretion) have been reported in association with racemic citalopram All patients with these events have recovered with discontinuation of escitalopram or citalopram and/or medical intervention Hyponatremia and SIADH have also been reported in association with other marketed drugs effective in the treatment of major depressive disorder

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 treated with placebo One additional case of hypomania has been reported 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

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

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

Use in Patients with Concomitant Illness

Clinical experience with escitalopram in patients with certain concomitant systemic illnesses is limited Caution is advisable in using escitalopram in patients with diseases or conditions that produce altered metabolism or hemodynamic responses

Escitalopram has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing

In subjects with hepatic impairment, clearance of racemic citalopram was decreased and plasma concentrations were increased. The recommended dose of escitalopram in hepatically impaired patients is 10 mg/day (see **DOSAGE AND ADMINISTRATION**)

Because escitalopram is extensively metabolized excretion of unchanged drug in urine is a minor route of elimination Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with escitalopram however it should be used with caution in such patients (see **DOSAGE AND ADMINISTRATION**)

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe escitalopram

In a study in normal volunteers escitalopram 10 mg/day did not impair psychomotor performance The effect of escitalopram on psychomotor coordination judgment or thinking has not been systematically examined in controlled studies Because psychoactive drugs may impair judgment thinking or motor skills 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

Patients should be told that although escitalopram has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol the concomitant use of escitalopram and alcohol in depressed patients is not advised

Patients should be made aware that escitalopram is the active isomer of citalopram hydrobromide and that the two medications should not be taken concomitantly

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over the-counter drugs as there is a potential for interactions

Patients should be cautioned about the concomitant use of escitalopram and NSAIDs aspirin or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding

Patients should be advised [illegible] increased feeding [illegible]

While patients may notice improvement with escitalopram therapy in 1 to 4 weeks they should be advised to continue therapy as directed

Patients and their families should be encouraged to be alert to the emergence of anxiety agitation panic attacks insomnia irritability hostility impulsivity akathisia hypomania mania worsening of depression and suicidal ideation especially early during antidepressant treatment Such symptoms should be reported to the patient's physician especially if they are severe abrupt in onset or were not part of the patient's presenting symptoms

Laboratory Tests

There are no specific laboratory tests recommended

Concomitant Administration with Racemic Citalopram

Citalopram Since escitalopram is the active isomer of racemic citalopram the two agents should not be coadministered

Drug Interactions

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

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

Monoamine Oxidase Inhibitors (MAOIs) See **CONTRAINDICATIONS** and **WARNINGS**

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 potentiated the risk of bleeding. Thus patients should be cautioned about the use of such drugs concurrently with escitalopram

Cimetidine In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of 400 mg/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

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

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

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 an SSRI (e g fluoxetine fluvoxamine paroxetine sertraline citalopram, escitalopram) is clinically warranted appropriate observation of the patient is advised

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

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

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

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

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

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

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

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 not significantly different in poor metabolizers and extensive 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

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 beta adrenergic blocker metoprolol (given in a single dose of 100 mg) Increased metoprolol plasma levels have been associated with decreased cardioselectivity Coadministration of escitalopram and metoprolol had no clinically significant effects on blood pressure or heart rate

Electroconvulsive Therapy (ECT) There are no clinical studies of the combined use of ECT and escitalopram

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Racemic citalopram was administered in the diet to NMRI/BOM strain mice and COBS WI strain rats for 18 and 24 months respectively There was no evidence for carcinogenicity of racemic citalopram in mice receiving up to 240 mg/kg/day There was an increased incidence of small intestine carcinoma in rats receiving 8 or 24 mg/kg/day racemic citalopram A no-effect dose for this finding was not established. The relevance of these findings to humans is unknown

Mutagenesis

Racemic citalopram was mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) in 2 of 5 bacterial strains (Salmonella TA98 and TA1537) in the absence of metabolic activation It was clastogenic in the *in vitro* Chinese hamster lung cell assay for chromosomal aberrations in the presence and absence of metabolic activation. Racemic citalopram was not mutagenic in the *in vitro* mammalian forward gene mutation assay (HPRT) in mouse lymphoma cells or in a coupled *in vitro/in vivo* unscheduled DNA synthesis (UDS) assay in rat liver It was not clastogenic in the *in vitro* chromosomal aberration assay in human lymphocytes or in two *in vivo* mouse micronucleus assays.

Impairment of Fertility

When racemic citalopram was administered orally to 16 male and 24 female rats prior to and throughout mating and gestation at doses of 32 48 and 72 mg/kg/day mating was decreased at all doses and fertility was decreased at doses ≥ 32 mg/kg/day Gestation duration was increased at 48 mg/kg/day

Pregnancy

Pregnancy Category C

In a rat embryo/fetal 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 at 56 mg/kg/day was present at all dose levels The developmental no-effect dose of 56 mg/kg/day is 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 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 animal reproduction studies racemic citalopram has been shown to have adverse effects on embryo/fetal and postnatal development, including teratogenic effects when administered at doses greater than human therapeutic doses

In two rat embryo/fetal 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 embryo/fetal 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 decreased body weight gain) The developmental no-effect dose was 56 mg/kg/day In a rabbit study no adverse effects on embryo/fetal 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 A no-effect dose was not determined in that study

Pregnancy Nonteratogenic Effects Neonates exposed to escitalopram and other SSRIs or 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 hypotonia 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**)

When treating a pregnant woman with escitalopram during the third trimester the physician should carefully consider the potential risks and benefits of treatment (see **DOSAGE AND ADMINISTRATION**)

Labor and Delivery

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

Nursing Mothers

Racemic citalopram, like many other drugs is excreted in human breast milk There have been two reports of infants experiencing excessive somnolence decreased feeding, and weight loss in association with breast feeding from a citalopram-treated mother in one case the infant was reported to recover completely upon discontinuation of citalopram by its mother and in the second case no follow-up information was available The decision whether to continue or discontinue either nursing or escitalopram therapy should take into account the risks of citalopram exposure for the infant and the benefits of escitalopram treatment for the mother

Pediatric Use

Safety and effectiveness in pediatric patients have not been established (see **WARNINGS Clinical Worsening and Suicide Risk**)

Geriatric Use

Approximately 6% of the 1144 patients receiving escitalopram in controlled trials of escitalopram were 60 years of age or older elderly patients in these trials received daily doses of escitalopram between 10 and 20 mg The number of elderly patients in these trials was insufficient to adequately assess for possible differential efficacy and safety measures on the basis of age Nevertheless greater sensitivity of some elderly individuals to effects of escitalopram cannot be ruled out

In two pharmacokinetic studies, escitalopram half-life was increased by approximately 50% in elderly subjects as compared to young subjects and C_{max} was unchanged (see **CLINICAL PHARMACOLOGY**) 10 mg/day is the recommended dose for elderly patients (see **DOSAGE AND ADMINISTRATION**)

Of 4422 patients in clinical studies of racemic citalopram, 1357 were 60 and over 1034 were 65 and over and 457 were 75 and over No overall differences in safety or effectiveness were observed between these subjects and younger subjects and other reported clinical experience has not identified differences in responses between the elderly and younger patients but again greater sensitivity of some elderly individuals cannot be ruled out

ADVERSE REACTIONS

Adverse event information for escitalopram was collected from 715 patients with major depressive disorder who were exposed to escitalopram and from 592 patients who were exposed to placebo in double-blind placebo-controlled trials An additional 284 patients with major depressive disorder were newly exposed to escitalopram in open-label trials

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing Consequently it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories In the tables and tabulations that follow standard World Health Organization (WHO) terminology has been used to classify reported adverse events

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once a treatment-emergent adverse event of the type listed An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation

Adverse Events Associated with Discontinuation of Treatment

Major Depressive Disorder

Among the 715 depressed patients who received escitalopram in placebo-controlled trials, 6% discontinued treatment due to an adverse event as compared to 2% of 592 patients receiving placebo In two fixed dose studies the rate of discontinuation for adverse events in patients receiving 10 mg/day escitalopram was not significantly different from the rate of discontinuation for adverse events in patients receiving placebo The rate of discontinuation for adverse events in patients assigned to a fixed dose of 20 mg/day escitalopram was 10% which was significantly different from the rate of discontinuation for adverse events in patients receiving 10 mg/day escitalopram (4%) and placebo (3%) Adverse events that were associated with the discontinuation of at least 1% of patients treated with escitalopram, and for which the rate was at least twice the placebo rate were nausea (2%) and ejaculation disorder (2% of male patients)

Incidence of Adverse Events in Placebo-Controlled Clinical Trials

Major Depressive Disorder

Table 1 enumerates the incidence rounded to the nearest percent of treatment-emergent adverse events that occurred among 715 depressed patients who received escitalopram at doses ranging from 10 to 20 mg/day in placebo-controlled trials Events included are those occurring in 2% or more of patients treated with escitalopram and for which the incidence in patients treated with escitalopram was greater than the incidence in placebo-treated patients

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials Similarly the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments uses and investigators The cited figures however do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied

The most commonly observed adverse events in escitalopram patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were insomnia, ejaculation disorder (primarily ejaculatory delay) nausea sweating increased fatigue and somnolence (see TABLE 1)

TABLE 1
Treatment Emergent Adverse Events.
Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder*

(Percentage of Patients Reporting Event)

Body System / Adverse Event	Escitalopram (N=715)	Placebo (N=592)
Autonomic Nervous System Disorders		
Dry Mouth	6%	5%
Sweating Increased	5%	2%
Central & Peripheral Nervous System Disorders		
Dizziness	5%	3%
Gastrointestinal Disorders		
Nausea	15%	7%
Diarrhea	8%	5%
Constipation	3%	1%
Indigestion	3%	1%
Abdominal Pain	2%	1%
General		
Influenza like Symptoms	5%	4%
Fatigue	5%	2%
Psychiatric Disorders		
Insomnia	9%	4%
Somnolence	6%	2%
Appetite Decreased	3%	1%
Libido Decreased	3%	1%
Respiratory System Disorders		
Rhinitis	5%	4%
Sinusitis	3%	2%
Urogenital		
Ejaculation Disorder[1,2]	9%	<1%
Impotence[2]	3%	<1%
Anorgasmia[3]	2%	<1%

*Events reported by at least 2% of patients treated with escitalopram are reported except for the following events which had an incidence on placebo ≥ escitalopram headache upper respiratory tract infection back pain pharyngitis inflicted injury anxiety

[1]Primarily ejaculatory delay
[2]Denominator used was for males only (N=225 escitalopram N=188 placebo)
[3]Denominator used was for females only (N=490 escitalopram, N=404 placebo)

Dose Dependency of Adverse Events

The potential dose dependency of common adverse events (defined as an incidence rate of ≥ 5% in either the 10 mg or 20 mg escitalopram groups) was examined on the basis of the combined incidence of adverse events in two fixed dose trials The overall incidence rates of adverse events in 10 mg escitalopram-treated patients (66%) was similar to that of the placebo treated patients (61%) while the incidence rate in 20 mg/day escitalopram-treated patients was greater (86%) Table 2 shows common adverse events that occurred in the 20 mg/day escitalopram group with an incidence that was approximately twice that of the 10 mg/day escitalopram group and approximately twice that of the placebo group

[illegible] 10 mg/day escitalopram or 20 mg/day escitalopram

Adverse Event	Placebo (N=311)	10 mg/day escitalopram (N=310)	20 mg/day escitalopram (N=125)
Insomnia	4%	7%	14%
Diarrhea	5%	6%	14%
Dry Mouth	3%	4%	9%
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%

Adverse events with an incidence rate of at least 5% in either of the escitalopram groups and with an incidence rate in the 20 mg/day escitalopram group that was approximately twice that of the 10 mg/day escitalopram group and the placebo group

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 3 shows the incidence rates of sexual side effects in patients in placebo-controlled trials

TABLE 3
Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials

Adverse Event	Escitalopram	Placebo
	In Males Only	
	(N=407)	(N=383)
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) racemic citalopram (N=351) and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables These analyses revealed (1) a decrease in heart rate of 2 2 bpm for escitalopram and 2 7 bpm for racemic citalopram, compared to an increase of 0 3 bpm for placebo and (2) an increase in QTc interval of 3 9 msec for escitalopram and 3 7 msec for racemic citalopram, compared to 0 5 msec for placebo Neither escitalopram nor racemic citalopram were associated with the development of clinically significant ECG abnormalities

Other Events Observed During the Premarketing Evaluation of Escitalopram

Following is a list of WHO terms that reflect 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 open-label clinical trials during its premarketing evaluation All reported events are included except those already listed in Table 1 those occurring in only one patient event terms that are so general as to be uninformative and those that are unlikely to be drug related It is important to emphasize that although the events reported occurred during treatment with escitalopram, they were not necessarily caused by it

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions frequent adverse events are those occurring on one or more occasions in at least 1/100 patients, infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients

Cardiovascular *Frequent* palpitation hypertension *Infrequent* bradycardia, tachycardia, ECG abnormal flushing varicose vein

Central and Peripheral Nervous System Disorders *Frequent* light-headed feeling migraine *Infrequent* tremor vertigo restless legs shaking, twitching dysequilibrium tics carpal tunnel syndrome muscle contractions involuntary sluggishness coordination abnormal faintness hyperreflexia, muscular tone increased

Gastrointestinal Disorders *Frequent* heartburn abdominal cramp gastroenteritis *Infrequent* gastroesophageal reflux, bloating abdominal discomfort, dyspepsia increased stool frequency belching, gastritis hemorrhoids gagging, polyposis gastric swallowing difficult

General *Frequent* allergy pain in limb fever hot flushes, chest pain *Infrequent* edema of extremities chills tightness of chest leg pain asthenia syncope malaise anaphylaxis fall

Hemic and Lymphatic Disorders *Infrequent* bruise anemia nosebleed hematoma, lymphadenopathy cervical

Metabolic and Nutritional Disorders *Frequent* increased weight, *Infrequent* decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia.

Musculoskeletal System Disorders *Frequent* arthralgia, myalgia, *Infrequent* jaw stiffness muscle cramp muscle stiffness, arthritis, muscle weakness, back discomfort, arthropathy jaw pain, joint stiffness

Psychiatric Disorders *Frequent* appetite increased, lethargy irritability concentration impaired. *Infrequent* jitteriness panic reaction, agitation, apathy forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, bruxism, carbohydrate craving, confusion, depersonalization disorientation emotional lability feeling unreal, tremulousness nervous crying abnormal depression excitability auditory hallucination suicidal tendency

Reproductive Disorders/Female *Frequent* menstrual cramps menstrual disorder *Infrequent* menorrhagia, breast neoplasm, pelvic inflammation premenstrual syndrome spotting between menses

*% based on female subjects only N=905

Respiratory System Disorders *Frequent* bronchitis sinus congestion coughing, nasal congestion sinus headache *Infrequent* asthma, breath shortness, laryngitis pneumonia, tracheitis

Skin and Appendages Disorders *Frequent* rash *Infrequent* pruritus acne alopecia, eczema, dermatitis dry skin, folliculitis, lipoma, furunculosis dry lips skin nodule

Special Senses *Frequent* vision blurred, tinnitus *Infrequent* taste alteration earache conjunctivitis, vision abnormal dry eyes eye irritation visual disturbance eye infection pupils dilated metallic taste

Urinary System Disorders *Frequent* urinary frequency urinary tract infection *Infrequent* urinary urgency kidney stone dysuria, blood in urine

Events Reported Subsequent to the Marketing of Racemic Citalopram and Escitalopram

Although no causal relationship to racemic citalopram or escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with racemic citalopram treatment and with escitalopram treatment during postmarketing experience and were not observed during the premarketing evaluation of citalopram or escitalopram acute renal failure angioedema toxic epidermal necrolysis gastrointestinal hemorrhage grand mal seizures (or convulsions) neuroleptic malignant syndrome pancreatitis QT prolongation rhabdomyolysis serotonin syndrome thrombocytopenia, torsades de pointes

Events Reported Subsequent to Marketing of Racemic Citalopram (not observed during the postmarketing experience with escitalopram)

Although no causal relationship to racemic citalopram treatment has been found the following adverse events have been reported to have occurred in patients and to be temporally associated with racemic citalopram treatment and were not observed during the premarketing evaluation of citalopram akathisia, allergic reaction anaphylaxis choreoathetosis delirium, dyskinesia ecchymosis erythema multiforme hemolytic anemia hepatic necrosis myoclonus nystagmus priapism, prolactinemia prothrombin decreased spontaneous abortion thrombosis and ventricular arrhythmia

Events Reported Subsequent to Marketing of Escitalopram (not observed during the postmarketing experience with citalopram)
Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with escitalopram treatment and were not observed during the premarketing evaluation of escitalopram: aggression, atrial fibrillation, seizures, diplopia, dystonia, extrapyramidal disorders, abnormal gait, visual hallucinations, hepatitis, hypotension, myocardial infarction, orthostatic hypotension, pulmonary embolism, SIADH, ventricular tachycardia.

DRUG ABUSE AND DEPENDENCE
Controlled Substance Class
Escitalopram is not a controlled substance.

Physical and Psychological Dependence
Animal studies suggest that the abuse liability of racemic citalopram is low. Escitalopram has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. The premarketing clinical experience with escitalopram did not reveal any drug-seeking behavior. However, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate escitalopram patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE
Human Experience
There have been reports of escitalopram overdose involving doses of up to 600 mg. All patients recovered and no symptoms associated with the overdoses were reported. In clinical trials of racemic citalopram, there were no reports of fatal citalopram overdose involving overdoses of up to 2000 mg. During the postmarketing evaluation of citalopram, like other SSRIs, a fatal outcome in a patient who has taken an overdose of citalopram has been rarely reported.

Postmarketing reports of drug overdoses involving citalopram have included 12 fatalities, 10 in combination with other drugs and/or alcohol and 2 with citalopram alone (3920 mg and 2800 mg), as well as non-fatal overdoses of up to 6000 mg. Symptoms most often accompanying citalopram overdose, alone or in combination with other drugs and/or alcohol, included dizziness, sweating, nausea, vomiting, tremor, somnolence, sinus tachycardia, and convulsions. In more rare cases, observed symptoms included amnesia, confusion, coma, hyperventilation, cyanosis, rhabdomyolysis, and ECG changes (including QTc prolongation, nodal rhythm, ventricular arrhythmia, and one possible case of torsades de pointes).

Management of Overdose
Establish and maintain an airway to ensure adequate ventilation and oxygenation. Gastric evacuation by lavage and use of activated charcoal should be considered. Careful observation and cardiac and vital sign monitoring are recommended, along with general symptomatic and supportive care. Due to the large volume of distribution of escitalopram, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. There are no specific antidotes for escitalopram.

In managing overdosage, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

DOSAGE AND ADMINISTRATION
Major Depressive Disorder
Initial Treatment
The recommended dose of escitalopram is 10 mg once daily. A fixed-dose trial of escitalopram demonstrated the effectiveness of both 10 mg and 20 mg of escitalopram, but failed to demonstrate a greater benefit of 20 mg over 10 mg (see **Clinical Efficacy Trials** under **CLINICAL PHARMACOLOGY**). If the dose is increased to 20 mg, this should occur after a minimum of one week.

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

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 should be used with caution in patients with severe renal impairment.

Treatment of Pregnant Women During the Third Trimester
Neonates exposed to escitalopram and other SSRIs or SNRIs, late in the third trimester, have developed complications requiring long hospitalization, respiratory support, and tube feeding (see **PRECAUTIONS**). When treating pregnant women with escitalopram during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering escitalopram in the third trimester.

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 10 or 20 mg/day for periods of up to 36 weeks in patients with major depressive disorder who responded while taking escitalopram during an 8-week, acute-treatment phase demonstrated a benefit of such maintenance treatment (see **Clinical Efficacy Trials** under **CLINICAL PHARMACOLOGY**). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

Discontinuation of Treatment with Escitalopram
Symptoms associated with discontinuation of escitalopram and other SSRIs and SNRIs have been reported (see **PRECAUTIONS**). 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.

Switching Patients To or From a Monoamine Oxidase Inhibitor
At least 14 days should elapse between discontinuation of an MAOI and initiation of escitalopram therapy. Similarly, at least 14 days should be allowed after stopping escitalopram before starting an MAOI (see **CONTRAINDICATIONS** and **WARNINGS**).

HOW SUPPLIED
Escitalopram oxalate capsules are available as follows:

10 mg[1], grey body, dark grey cap printed in black with "EC 10" and "G"

Bottles of 100 NDC 57315-101-02
Bottles of 1000 NDC 57315-101-03

20 mg[1], ivory body, brown cap printed in black with "EC 20" and "G"

Bottles of 100 NDC 57315-102-02
Bottles of 1000 NDC 57315-102-03

[1] Escitalopram base equivalent

Store at 25°C (77°F), excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature).

Dispense in tight, light-resistant containers as described in the USP.

ANIMAL TOXICOLOGY
Retinal Changes in Rats
Pathologic changes (degeneration/atrophy) were observed in the retinas of albino rats in the 2-year carcinogenicity study with racemic citalopram. There was an increase in both incidence and severity of retinal pathology in both male and female rats receiving 80 mg/kg/day. Similar findings were not present in rats receiving 24 mg/kg/day of racemic citalopram for two years, in mice receiving up to 240 mg/kg/day of racemic citalopram for 18 months, or in dogs receiving up to 20 mg/kg/day of racemic citalopram for one year.

Additional studies to investigate the mechanism for this pathology have not been performed, and the potential significance of this effect in humans has not been established.

Cardiovascular Changes in Dogs
In a one-year toxicology study, 5 of 10 beagle dogs receiving oral racemic citalopram doses of 8 mg/kg/day died suddenly between weeks 17 and 31 following initiation of treatment. Sudden deaths were not observed in rats at doses of racemic citalopram up to 120 mg/kg/day, which produced plasma levels of citalopram and its metabolites demethylcitalopram and didemethylcitalopram (DDCT) similar to those observed in dogs at 8 mg/kg/day. A subsequent intravenous dosing study demonstrated that in beagle dogs, racemic DDCT caused QT prolongation, a known risk factor for the observed outcome in dogs.

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