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PRESCRIBING INFORMATION

Paroxetine Tablets, USP

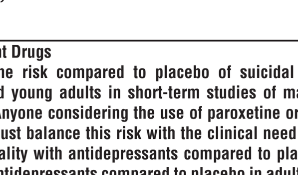
Rx Only

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 paroxetine 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. Paroxetine tablets are not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

DESCRIPTION

Paroxetine hydrochloride, USP is an orally administered psychotropic drug. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (3S-trans)-3-[(1,3-Benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)-piperidine hydrochloride hemihydrate and has the molecular formula of $C_{19}H_{20}FNO_3 \cdot HCl \cdot {}_{1/2}H_2O$. The molecular weight is 374.8 (329.4 as free base). The structural formula of paroxetine hydrochloride is:



Paroxetine hydrochloride, USP is a white or almost white, crystalline powder slightly soluble in water, soluble in methanol and alcohol.

Each film-coated tablet contains paroxetine hydrochloride hemihydrate, USP equivalent to paroxetine as follows: 10 mg-white (scored); 20 mg-white (scored); 30 mg–blue, 40 mg–white. Inactive ingredients consist of dibasic calcium phosphate dihydrate, pregelatinized starch, sodium starch glycolate type A, magnesium stearate, hypromellose, titanium dioxide, macrogol and FD&C Blue #2 and polysorbate 80.

CLINICAL PHARMACOLOGY

Pharmacodynamics: The efficacy of paroxetine in the treatment of major depressive disorder, social anxiety disorder, obsessive compulsive disorder (OCD), panic disorder (PD), and generalized anxiety disorder (GAD) is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT). Studies at clinically relevant doses in humans have demonstrated that paroxetine blocks the uptake of serotonin into human platelets. In vitro studies in animals also suggest that paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. In vitro radioligand binding studies indicate that paroxetine has little affinity for muscarinic, alpha$_1$-, alpha$_2$-, beta-adrenergic-, dopamine (D_2)-, 5-HT$_1$-, 5-HT$_2$-, and histamine (H_1)-receptors; antagonism of muscarinic, histaminergic, and alpha$_1$-adrenergic receptors has been associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs.

Because the relative potencies of paroxetine's major metabolites are at most 1/50 of the parent compound, they are essentially inactive.

Pharmacokinetics: Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. The mean elimination half-life is approximately 21 hours (CV 32%) after oral dosing of 30 mg tablets of paroxetine daily for 30 days. Paroxetine is extensively metabolized and the metabolites are considered to be inactive. Nonlinearity in pharmacokinetics is observed with increasing doses. Paroxetine metabolism is mediated in part by CYP2D6, and the metabolites are primarily excreted in the urine and to some extent in the feces. Pharmacokinetic behavior of paroxetine has not been evaluated in subjects who are deficient in CYP2D6 (poor metabolizers).

In a meta-analysis of paroxetine from 4 studies done in healthy volunteers following multiple dosing of 20 mg/day to 40 mg/day, males did not exhibit a significantly lower C_{max} or AUC than females.

Absorption and Distribution:

Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. In a study in which normal male subjects (n = 15) received 30 mg tablets daily for 30 days, steady-state paroxetine concentrations were achieved by approximately 10 days for most subjects, although it may take substantially longer in an occasional patient. At steady-state, mean values of C_{max}, T_{max}, C_{min}, and $T_{1/2}$ were 61.7 ng/mL (CV 45%), 5.2 hr. (CV 10%), 30.7 ng/mL (CV 67%), and 21.0 hours (CV 32%), respectively. The steady-state C_{max} and C_{min} values were about 6 and 14 times what would be predicted from single-dose studies. Steady-state drug exposure based on AUC_{0-24} was about 8 times greater than would have been predicted from single-dose data in these subjects. The excess accumulation is a consequence of the fact that 1 of the enzymes that metabolizes paroxetine is readily saturable.

The effects of food on the bioavailability of paroxetine were studied in subjects administered a single dose with and without food. AUC was only slightly increased (6%) when drug was administered with food but the C_{max} was 29% greater, while the time to reach peak plasma concentration decreased from 6.4 hours post-dosing to 4.9 hours.

Paroxetine distributes throughout the body, including the CNS, with only 1% remaining in the plasma.

Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/mL and 400 ng/mL, respectively. Under clinical conditions, paroxetine concentrations would normally be less than 400 ng/mL. Paroxetine does not alter the in vitro protein binding of phenytoin or warfarin.

Metabolism and Excretion: The mean elimination half-life is approximately 21 hours (CV 32%) after oral dosing of 30 mg tablets daily for 30 days of paroxetine. In steady-state dose proportionality studies involving elderly and nonelderly patients, at doses of 20 mg to 40 mg daily for the elderly and 20 mg to 50 mg daily for the nonelderly, some nonlinearity was observed in both populations, again reflecting a saturable metabolic pathway. In comparison to C_{min} values after 20 mg daily, values after 40 mg daily were only about 2 to 3 times greater than doubled.

Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by CYP2D6. Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of this enzyme in paroxetine metabolism also suggests potential drug-drug interactions (see PRECAUTIONS: Drugs Metabolized by CYP2D6).

Approximately 64% of a 30 mg oral solution dose of paroxetine was excreted in the urine with 2% as the parent compound and 62% as metabolites over a 10-day post-dosing period. About 36% was excreted in the feces (probably via the bile), mostly as metabolites and less than 1% as the parent compound over the 10-day post-dosing period.

Other Clinical Pharmacology Information: ***Specific Populations: Renal and Liver Disease:*** Increased plasma concentrations of paroxetine occur in subjects with renal and hepatic impairment. The mean plasma concentrations in patients with creatinine clearance below 30 mL/min. were approximately 4 times greater than seen in normal volunteers. Patients with creatinine clearance of 30 to 60 mL/min. and patients with hepatic functional impairment had about a 2-fold increase in plasma concentrations (AUC, C_{max}).

The initial dosage should therefore be reduced in patients with severe renal or hepatic impairment, and upward titration, if necessary, should be at increased intervals (see DOSAGE AND ADMINISTRATION).

Elderly Patients: In a multiple-dose study in the elderly at daily paroxetine doses of 20, 30, and 40 mg, C_{min} concentrations were about 70% to 80% greater than the respective C_{min} concentrations in nonelderly subjects. Therefore the initial dosage in the elderly should be reduced (see DOSAGE AND ADMINISTRATION).

Drug-Drug Interactions: In vitro drug interaction studies reveal that paroxetine inhibits CYP2D6. Clinical drug interaction studies have been performed with substrates of CYP2D6 and show that paroxetine can inhibit the metabolism of drugs metabolized by CYP2D6 including desipramine, risperidone, and atomoxetine (see PRECAUTIONS: Drug Interactions).

Clinical Trials

Major Depressive Disorder: The efficacy of paroxetine as a treatment for major depressive disorder has been established in 6 placebo-controlled studies of patients with major depressive disorder (aged 18 to 73). In these studies, paroxetine was shown to be significantly more effective than placebo in treating major depressive disorder by at least 2 of the following measures: Hamilton Depression Rating Scale (HDRS), the Hamilton depressed mood item, and the Clinical Global Impression (CGI)-Severity of Illness. Paroxetine was significantly better than placebo in improvement of the HDRS sub-factor scores, including the depressed mood item, sleep disturbance factor, and anxiety factor.

A study of outpatients with major depressive disorder who had responded to paroxetine (HDRS total score <8) during an initial 8-week open-treatment phase and were then randomized to continuation on paroxetine or placebo for 1 year demonstrated a significantly lower relapse rate for patients taking paroxetine (15%) compared to those on placebo (39%). Effectiveness was similar for male and female patients.

Obsessive Compulsive Disorder: The effectiveness of paroxetine in the treatment of obsessive compulsive disorder (OCD) was demonstrated in two 12-week multicenter placebo-controlled studies of adult outpatients (Studies 1 and 2). Patients in all studies had moderate to severe OCD (DSM-IIIR) with mean baseline ratings on the Yale Brown Obsessive Compulsive Scale (YBOCS) total score ranging from 23 to 26. Study 1, a dose-range finding study where patients were treated with fixed doses of 20, 40, or 60 mg of paroxetine/day demonstrated that daily doses of paroxetine 40 and 60 mg are effective in the treatment of OCD. Patients receiving doses of 40 and 60 mg paroxetine experienced a mean reduction of approximately 6 and 7 points, respectively, on the YBOCS total score which was significantly greater than the approximate 4-point reduction at 20 mg and a 3-point reduction in the placebo-treated patients. Study 2 was a flexible-dose study comparing paroxetine (20 to 60 mg daily) with clomipramine (25 to 250 mg daily). In this study, patients receiving paroxetine experienced a mean reduction of approximately 7 points on the YBOCS total score, which was significantly greater than the mean reduction of approximately 4 points in placebo-treated patients.

The following table provides the outcome classification by treatment group on Global Improvement items of the Clinical Global Impression (CGI) scale for Study 1.

Outcome Classification (%) on CGI-Global Improvement Item for Completers in Study 1				
Outcome Classification	Placebo (n = 74)	Paroxetine 20 mg (n = 75)	Paroxetine 40 mg (n = 66)	Paroxetine 60 mg (n = 66)
Worse	14%	7%	7%	3%
No Change	44%	35%	22%	19%
Minimally Improved	24%	33%	29%	34%
Much Improved	11%	18%	22%	24%
Very Much Improved	7%	7%	20%	20%

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

The long-term maintenance effects of paroxetine in OCD were demonstrated in a long-term extension to Study 1. Patients who were responders on paroxetine during the 3-month double-blind phase and a 6-month extension on open-label paroxetine (20 to 60 mg/day) were randomized to either paroxetine or placebo in a 6-month double-blind relapse prevention phase. Patients randomized to paroxetine were significantly less likely to relapse than comparably treated patients who were randomized to placebo.

Panic Disorder: The effectiveness of paroxetine in the treatment of panic disorder was demonstrated in three 10- to 12-week multicenter, placebo-controlled studies of adult outpatients (Studies 1-3). Patients in all studies had panic disorder (DSM-IIIR), with or without agoraphobia. In these studies, paroxetine was shown to be significantly more effective than placebo in treating panic disorder by at least 2 out of 3 measures of panic attack frequency and on the Clinical Global Impression Severity of Illness score.

Study 1 was a 10-week dose-range finding study; patients were treated with fixed paroxetine doses of 10, 20, or 40 mg/day or placebo. A significant difference from placebo was observed only for the 40 mg/day group. At endpoint, 76% of patients receiving paroxetine 40 mg/day were free of panic attacks, compared to 44% of placebo-treated patients.

Study 2 was a 12-week flexible-dose study comparing paroxetine (10 to 60 mg daily) and placebo. At endpoint, 51% of paroxetine patients were free of panic attacks compared to 32% of placebo-treated patients.

Study 3 was a 12-week flexible-dose study comparing paroxetine (10 to 60 mg daily) to placebo in patients concurrently receiving standardized cognitive behavioral therapy. At endpoint, 33% of the paroxetine-treated patients showed a reduction to 0 or 1 panic attacks compared to 14% of placebo patients.

In both Studies 2 and 3, the mean paroxetine dose for completers at endpoint was approximately 40 mg/day of paroxetine.

Long-term maintenance effects of paroxetine in panic disorder were demonstrated in an extension to Study 1. Patients who were responders during the 10-week double-blind phase and during a 3-month double-blind extension phase were randomized to either paroxetine (10, 20, or 40 mg/day) or placebo in a 3-month double-blind relapse prevention phase. Patients randomized to paroxetine were significantly less likely to relapse than comparably treated patients who were randomized to placebo.

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

Social Anxiety Disorder: The effectiveness of paroxetine in the treatment of social anxiety disorder was demonstrated in three 12-week, multicenter, placebo-controlled studies (Studies 1, 2, and 3) of adult outpatients with social anxiety disorder (DSM-IV). In these studies, the effectiveness of paroxetine compared to placebo was evaluated on the basis of (1) the proportion of responders, as defined by a Clinical Global Impression (CGI) Improvement score of 1 (very much improved) or 2 (much improved), and (2) change from baseline in the Liebowitz Social Anxiety Scale (LSAS).

Studies 1 and 2 were flexible-dose studies comparing paroxetine (20 to 50 mg daily) and placebo. Paroxetine demonstrated statistically significant superiority over placebo on both the CGI Improvement responder criterion and the Liebowitz Social Anxiety Scale (LSAS). In Study 1, for patients who completed to week 12, 69% of paroxetine-treated patients compared to 29% of placebo-treated patients were CGI Improvement responders. In Study 2, CGI Improvement responders were 77% and 42% for the paroxetine- and placebo-treated patients, respectively.

Study 3 was a 12-week study comparing fixed paroxetine doses of 20, 40, or 60 mg/day with placebo. Paroxetine 20 mg was demonstrated to be significantly superior to placebo on both the LSAS Total Score and the CGI Improvement responder criterion; there were trends for superiority over placebo for the 40 mg and 60 mg/day dose groups. There was no indication in this study of any additional benefit for doses higher than 20 mg/day.

Subgroup analyses generally did not indicate differences in treatment outcomes as a function of age, race, or gender.

Generalized Anxiety Disorder: The effectiveness of paroxetine in the treatment of Generalized Anxiety Disorder (GAD) was demonstrated in two 8-week, multicenter, placebo-controlled studies (Studies 1 and 2) of adult outpatients with Generalized Anxiety Disorder (DSM-IV).

Study 1 was an 8-week study comparing fixed paroxetine doses of 20 mg or 40 mg/day with placebo. Doses of 20 mg or 40 mg of paroxetine were both demonstrated to be significantly superior to placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score. There was not sufficient evidence in this study to suggest a greater benefit for the 40 mg/day dose compared to the 20 mg/day dose.

Study 2 was a flexible-dose study comparing paroxetine (20 mg to 50 mg daily) and placebo. Paroxetine demonstrated statistically significant superiority over placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score. A third study, also flexible-dose comparing paroxetine (20 mg to 50 mg daily), did not demonstrate statistically significant superiority of paroxetine over placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score, the primary outcome.

Subgroup analyses did not indicate differences in treatment outcomes as a function of race or gender. There were insufficient elderly patients to conduct subgroup analyses on the basis of age.

In a longer-term trial, 566 patients meeting DSM-IV criteria for Generalized Anxiety Disorder, who had responded during a single-blind, 8-week acute treatment phase with 20 to 50 mg/day of paroxetine, were randomized to continuation of paroxetine at their same dose, or to placebo, for up to 24 weeks of observation for relapse. Response during the single-blind phase was defined by having a decrease of ≥ 2 points compared to baseline on the CGI-Severity of Illness scale, to a score of ≤ 3. Relapse during the double-blind phase was defined as an increase of ≥ 2 points compared to baseline on the CGI-Severity of Illness scale to a score of ≥ 4, or withdrawal due to lack of efficacy. Patients receiving continued paroxetine experienced a significantly lower relapse rate over the subsequent 24 weeks compared to those receiving placebo.

INDICATIONS AND USAGE

Major Depressive Disorder: Paroxetine tablets, USP are indicated for the treatment of major depressive disorder.

The efficacy of paroxetine in the treatment of a major depressive episode was established in 6-week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder (see CLINICAL PHARMACOLOGY: Clinical Trials). A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: Change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The effects of paroxetine in hospitalized depressed patients have not been adequately studied.

The efficacy of paroxetine in maintaining a response in major depressive disorder for up to 1 year was demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY: Clinical Trials). Nevertheless, the physician who elects to use paroxetine tablets for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Obsessive Compulsive Disorder: Paroxetine tablets, USP are indicated for the treatment of obsessions and compulsions in patients with obsessive compulsive disorder (OCD) as defined in the DSM-IV. The obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of paroxetine was established in two 12-week trials with obsessive compulsive outpatients whose diagnoses corresponded most closely to the DSM-IIIR category of obsessive compulsive disorder (see CLINICAL PHARMACOLOGY: Clinical Trials).

Obsessive compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses, or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

Long-term maintenance of efficacy was demonstrated in a 6-month relapse prevention trial. In this trial, patients assigned to paroxetine showed a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY: Clinical Trials). Nevertheless, the physician who elects to use paroxetine tablets for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Panic Disorder: Paroxetine tablets, USP are indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

The efficacy of paroxetine was established in three 10- to 12-week trials in panic disorder patients whose diagnoses corresponded to the DSM-IIIR category of panic disorder (see CLINICAL PHARMACOLOGY: Clinical Trials).

Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which 4 (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

Long-term maintenance of efficacy was demonstrated in a 3-month relapse prevention trial. In this trial, patients with panic disorder assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY: Clinical Trials). Nevertheless, the physician who prescribes paroxetine tablets for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Social Anxiety Disorder: Paroxetine tablets, USP are indicated for the treatment of social anxiety disorder, also known as social phobia, as defined in DSM-IV (300.23). Social anxiety disorder is characterized by a marked and persistent fear of 1 or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. Exposure to the feared situation almost invariably provokes anxiety, which may approach the intensity of a panic attack. The feared situations are avoided or endured with intense anxiety or distress. The avoidance, anxious anticipation, or distress in the feared situation(s) interferes significantly with the person's normal routine, occupational or academic functioning, or social activities or relationships, or there is marked distress about having the phobias. Lesser degrees of performance anxiety or shyness generally do not require psychopharmacological treatment.

The efficacy of paroxetine was established in three 12-week trials in adult patients with social anxiety disorder (DSM-IV). Paroxetine has not been studied in children or adolescents with social phobia (see CLINICAL PHARMACOLOGY: Clinical Trials).

The effectiveness of paroxetine in long-term treatment of social anxiety disorder, i.e., for more than 12 weeks, has not been systematically evaluated in adequate and well-controlled trials. Therefore, the physician who elects to prescribe paroxetine tablets for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Generalized Anxiety Disorder: Paroxetine tablets, USP are indicated for the treatment of Generalized Anxiety Disorder (GAD), as defined in DSM-IV. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

The efficacy of paroxetine in the treatment of GAD was established in two 8-week placebo-controlled trials in adults with GAD. Paroxetine has not been studied in children or adolescents with Generalized Anxiety Disorder (see CLINICAL PHARMACOLOGY: Clinical Trials).

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 6 symptoms: Restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, sleep disturbance.

The efficacy of paroxetine in maintaining a response in patients with Generalized Anxiety Disorder, who responded during an 8-week acute treatment phase while taking paroxetine and were then observed for relapse during a period of up to 24 weeks, was demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY: Clinical Trials). Nevertheless, the physician who elects to use paroxetine tablets for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

The use of MAOIs intended to treat psychiatric disorders with paroxetine or within 14 days of stopping treatment with paroxetine is contraindicated because of an increased risk of serotonin syndrome. The use of paroxetine within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated (see WARNINGS and DOSAGE AND ADMINISTRATION).

Starting paroxetine in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome (see WARNINGS and DOSAGE AND ADMINISTRATION).

Concomitant use with thioridazine is contraindicated (see WARNINGS and PRECAUTIONS).

Concomitant use in patients taking pimozide is contraindicated (see PRECAUTIONS).

Paroxetine is contraindicated in patients with a hypersensitivity to paroxetine or any of the inactive ingredients in paroxetine tablets.

WARNINGS

Clinical Worsening and Suicide Risk: Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. 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 with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) 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 1,000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 Patients Treated
Increases Compared to Placebo	
<18	14 additional cases
18-24	5 additional cases
Decreases Compared to Placebo	
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 a course of drug therapy, 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 either 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 whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

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 Paroxetine, for a description of the risks of discontinuation of paroxetine).

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 healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for paroxetine 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 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 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 paroxetine is not approved for use in treating bipolar depression.

Serotonin Syndrome: The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including paroxetine, 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 drugs that impair metabolism of serotonin (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), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of paroxetine with MAOIs intended to treat psychiatric disorders is contraindicated. Paroxetine should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided 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. There may be circumstances when it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking paroxetine. Paroxetine should be discontinued before initiating treatment with the MAOI (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).

If concomitant use of paroxetine with certain other serotonergic drugs, i.e., triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, and St. John's Wort is clinically warranted, be aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

Treatment with paroxetine and any concomitant serotonergic agents should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Angle-Closure Glaucoma: The pupillary dilation that occurs following use of many antidepressant drugs including paroxetine may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

Potential Interaction with Thioridazine: Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias, and sudden death. This effect appears to be dose related.

An in vivo study suggests that drugs which inhibit CYP2D6, such as paroxetine, will elevate plasma levels of thioridazine. Therefore, it is recommended that paroxetine not be used in combination with thioridazine (see CONTRAINDICATIONS and PRECAUTIONS).

Usage in Pregnancy: ***Teratogenic Effects:*** Epidemiological studies have shown that infants exposed to paroxetine in the first trimester of pregnancy have an increased risk of congenital malformations, particularly cardiovascular malformations. The findings from these studies are summarized below:

- A study based on Swedish national registry data demonstrated that infants exposed to paroxetine during pregnancy (n = 815) had an increased risk of cardiovascular malformations (2% risk in paroxetine-exposed infants) compared to the entire registry population (1% risk), for an odds ratio (OR) of 1.8 (95% confidence interval 1.1 to 2.8). No increase in the risk of overall congenital malformations was seen in the paroxetine-exposed infants. The cardiac malformations in the paroxetine-exposed infants were primarily ventricular septal defects (VSDs) and atrial septal defects (ASDs). Septal defects range in severity from those that resolve spontaneously to those which require surgery.
- A separate retrospective cohort study from the United States (United Healthcare data) evaluated 5,956 infants of mothers dispensed antidepressants during the first trimester (n = 815 for paroxetine). This study showed a trend towards an increased risk for cardiovascular malformations for paroxetine (risk of 1.5%) compared to other antidepressants (risk of 1%), for an OR of 1.5 (95% confidence interval 0.8 to 2.9). Of the 12 paroxetine-exposed infants with cardiovascular malformations, 9 had VSDs. This study also suggested an increased risk of overall major congenital malformations including cardiovascular defects for paroxetine (4% risk) compared to other (2% risk) antidepressants (OR 1.8; 95% confidence interval 1.2 to 2.8).
- Two large case-control studies using separate databases, each with > 9,000 birth defect cases and > 4,000 controls, found that maternal use of paroxetine during the first trimester of pregnancy was associated with a 2- to 3-fold increased risk of right ventricular outflow tract obstructions. In one study the odds ratio was 2.5 (95% confidence interval, 1.0 to 6.0, 7 exposed infants) and in the other study the odds ratio was 3.3 (95% confidence interval, 1.3 to 8.8, 6 exposed infants).

Other studies have found varying results as to whether there was an increased risk of overall, cardiovascular, or specific congenital malformations. A meta-analysis of epidemiological data over a 16-year period (1992 to 2008) on first trimester paroxetine use in pregnancy and congenital malformations included the above-noted studies in addition to others (n = 17 studies that included overall malformations and n = 14 studies that included cardiovascular malformations; n = 20 distinct studies). While subject to limitations, this meta-analysis suggested an increased occurrence of cardiovascular malformations (prevalence odds ratio [POR] 1.5; 95% confidence interval 1.2 to 1.9) and overall malformations (POR 1.2; 95% confidence interval 1.1 to 1.4) with paroxetine use during the first trimester. It was not possible in this meta-analysis to determine the extent to which the observed prevalence of cardiovascular malformations might have contributed to that of overall malformations, nor was it possible to determine whether any specific types of cardiovascular malformations might have contributed to the observed prevalence of all cardiovascular malformations.

If a patient becomes pregnant while taking paroxetine, she should be advised of the potential harm to the fetus. Unless the benefits of paroxetine to the mother justify continuing treatment, consideration should be given to either discontinuing paroxetine therapy or switching to another antidepressant (see PRECAUTIONS: Discontinuation of Treatment With Paroxetine). For women who intend to become pregnant or are in their first trimester of pregnancy, paroxetine should only be initiated after consideration of the other available treatment options.

Animal Findings: Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately 8 (rat) and 2 (rabbit) times the maximum recommended human dose (MRHD) on an mg/m² basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg/day or approximately one-sixth of the MRHD on an mg/m² basis. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known.

Nonteratogenic Effects: Neonates exposed to paroxetine 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, hypotonia, hypertonia, 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: Serotonin Syndrome).

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 paroxetine) 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 paroxetine, 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 and ADVERSE REACTIONS: Postmarketing Reports).

PRECAUTIONS

General: ***Activation of Mania/Hypomania:*** During premarketing testing, hypomania or mania occurred in approximately 1.0% of unipolar patients treated with paroxetine compared to 1.1% of active-control and 0.3% of placebo-treated unipolar patients. In a subset of patients classified as bipolar, the rate of manic episodes was 2.2% for paroxetine and 11.6% for the combined active-control groups. As with all drugs effective in the treatment of major depressive disorder, paroxetine should be used cautiously in patients with a history of mania.

Seizures: During premarketing testing, seizures occurred in 0.1% of patients treated with paroxetine, a rate similar to that associated with other drugs effective in the treatment of major depressive disorder. Paroxetine should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Discontinuation of Treatment with Paroxetine: Recent clinical trials supporting the various approved indications for paroxetine employed a taper-phase regimen, rather than an abrupt discontinuation of treatment. The taper-phase regimen used in GAD clinical trials involved an incremental decrease in the daily dose by 10 mg/day at weekly intervals. When a daily dose of 20 mg/day was reached, patients were continued on this dose for 1 week before treatment was stopped.

With this regimen in those studies, the following adverse events were reported at an incidence of 2% or greater for paroxetine and were at least twice that reported for placebo: Abnormal dreams, paresthesia, and dizziness. In the majority of patients, these events were mild to moderate and were self-limiting and did not require medical intervention.

During marketing of paroxetine and other SSRIs and SNRIs, there have been spontaneous reports of adverse events occurring upon the 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 and tinnitus), 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 paroxetine. 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).

See also PRECAUTIONS: Pediatric Use, for adverse events reported upon discontinuation of treatment with paroxetine in pediatric patients.

Tamoxifen: Some studies have shown that the efficacy of tamoxifen, as measured by the risk of breast cancer relapse/mortality, may be reduced when co-prescribed with paroxetine as a result of paroxetine's irreversible inhibition of CYP2D6 (see Drug Interactions). However, other studies have failed to demonstrate such a risk. It is uncertain whether the coadministration of paroxetine and tamoxifen has a significant adverse effect on the efficacy of tamoxifen. One study suggests that the risk may increase with longer duration of coadministration. When tamoxifen is used for the treatment or prevention of breast cancer, prescribers should consider using an alternative antidepressant with little or no CYP2D6 inhibition.

Akathisia: The use of paroxetine or other SSRIs has been associated with the development of akathisia, which is characterized by an inner sense of restlessness and psychomotor agitation such as an inability to sit or stand still usually associated with subjective distress. This is most likely to occur within the first few weeks of treatment.

Hyponatremia: Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including paroxetine. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk (see PRECAUTIONS: Geriatric Use). Discontinuation of paroxetine should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, 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.

Abnormal Bleeding: SSRIs and SNRIs, including paroxetine, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake 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 paroxetine and NSAIDs, aspirin, or other drugs that affect coagulation.

Bone Fracture: Epidemiological studies on bone fracture risk following exposure to some antidepressants, including SSRIs, have reported an association between antidepressant treatment and fractures. There are multiple possible causes for this observation and it is unknown to what extent fracture risk is directly attributable to SSRI treatment. The possibility of a pathological fracture, that is, a fracture produced by minimal trauma in a patient with decreased bone mineral density, should be considered in patients treated with paroxetine who present with unexplained bone pain, point tenderness, swelling, or bruising.

Use in Patients with Concomitant Illness: Clinical experience with paroxetine in patients with certain concomitant systemic illness is limited. Caution is advisable in using paroxetine in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

As with other SSRIs, mydriasis has been infrequently reported in premarketing studies with paroxetine. A few cases of acute angle closure glaucoma associated with paroxetine therapy have been reported in the literature. As mydriasis can cause acute angle closure in patients with narrow angle glaucoma, caution should be used when paroxetine is prescribed for patients with narrow angle glaucoma.

Paroxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. Evaluation of electrocardiograms of 682 patients who received paroxetine in double-blind, placebo-controlled trials, however, did not indicate that paroxetine is associated with the development of significant ECG abnormalities. Similarly, paroxetine does not cause any clinically important changes in heart rate or blood pressure.

Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance < 30 mL/min.) or severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients: Paroxetine tablets should not be chewed or crushed, and should be swallowed whole.

Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of paroxetine and triptans, tramadol, or other serotonergic agents.

Patients should be advised that taking paroxetine can cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle closure glaucoma. Pre-existing glaucoma is almost always open-angle glaucoma because angle closure glaucoma, when diagnosed, can be treated definitively with iridectomy. Open-angle glaucoma is not a risk factor for angle closure glaucoma. Patients may wish to be examined to determine whether they are susceptible to angle closure, and have a prophylactic procedure (e.g., iridectomy), if they are susceptible.

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with paroxetine and should counsel them in its appropriate use. A patient Medication Guide is available for paroxetine tablets. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking paroxetine.

Clinical Worsening and Suicide Risk: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Drugs That Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin): Patients should be cautioned about the concomitant use of paroxetine and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding.

Interference with Cognitive and Motor Performance: Any psychoactive drug may impair judgment, thinking, or motor skills. Although in controlled studies paroxetine has not been shown to impair psychomotor performance, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with paroxetine does not affect their ability to engage in such activities.

Completing Course of Therapy: While patients may notice improvement with treatment with paroxetine in 1 to 4 weeks, they should be advised to continue therapy as directed.

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

Alcohol: Although paroxetine has not been shown to increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking paroxetine.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy (see WARNINGS: Usage in Pregnancy: *Teratogenic Effects* and *Nonteratogenic Effects*).

Nursing: Patients should be advised to notify their physician if they are breastfeeding an infant (see PRECAUTIONS: Nursing Mothers).

Laboratory Tests: There are no specific laboratory tests recommended.

Drug Interactions: ***Tryptophan:*** As with other serotonin reuptake inhibitors, an interaction between paroxetine and tryptophan may occur when they are coadministered. Adverse experiences, consisting primarily of headache, nausea, sweating, and dizziness, have been reported when tryptophan was administered to patients taking paroxetine. Consequently, concomitant use of paroxetine with tryptophan is not recommended (see WARNINGS: Serotonin Syndrome).

Monoamine Oxidase Inhibitors: See CONTRAINDICATIONS and WARNINGS.

Pimozide: In a controlled study of healthy volunteers, after paroxetine was titrated to 60 mg daily, co-administration of a single dose of 2 mg pimozide was associated with mean increases in pimozide AUC of 151% and C_{max} of 62%, compared to pimozide administered alone. The increase in pimozide AUC and C_{max} is due to the CYP2D6 inhibitory properties of paroxetine. Due to the narrow therapeutic index of pimozide and its known ability to prolong the QT interval, concomitant use of pimozide and paroxetine is contraindicated (see CONTRAINDICATIONS).

Serotonergic Drugs: Based on the mechanism of action of SNRIs and SSRIs, including paroxetine hydrochloride and the potential for serotonin syndrome, caution is advised when paroxetine is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, lithium, fentanyl, tramadol, or St. John's Wort (see WARNINGS: Serotonin Syndrome).

The concomitant use of paroxetine with MAOIs (including linezolid and intravenous methylene blue) is contradicated (see CONTRADICATIONS). The concomitant use of paroxetine with other SSRIs, SNRIs or tryptophan is not recommended (see PRECAUTIONS: Drug Interactions: *Tryptophan*).

Thioridazine: See CONTRAINDICATIONS and WARNINGS.

Warfarin: Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis in the face of unaltered prothrombin time) between paroxetine and warfarin. Since there is little clinical experience, the concomitant administration of paroxetine and warfarin should be undertaken with caution (see PRECAUTIONS: *Drugs That Interfere with Hemostasis).*

Triptans: There have been rare postmarketing reports of serotonin syndrome with the use of an SSRI and a triptan. If concomitant use of paroxetine with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see WARNINGS: Serotonin Syndrome).

Drugs Affecting Hepatic Metabolism: The metabolism and pharmacokinetics of paroxetine may be affected by the induction or inhibition of drug-metabolizing enzymes.

Cimetidine: Cimetidine inhibits many cytochrome P_{450} (oxidative) enzymes. In a study where paroxetine (30 mg once daily) was dosed orally for 4 weeks, steady-state plasma concentrations of paroxetine were increased by approximately 50% during coadministration with oral cimetidine (300 mg three times daily) for the final week. Therefore, when these drugs are administered concurrently, dosage adjustment of paroxetine after the 20 mg starting dose should be guided by clinical effect. The effect of paroxetine on cimetidine's pharmacokinetics was not studied.

Phenobarbital: Phenobarbital induces many cytochrome P_{450} (oxidative) enzymes. When a single oral 30 mg dose of paroxetine was administered at phenobarbital steady-state (100 mg once daily for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 25% and 38%, respectively) compared to paroxetine administered alone. The effect of paroxetine on phenobarbital pharmacokinetics was not studied. Since paroxetine exhibits nonlinear pharmacokinetics, the results of this study may not address the case where the 2 drugs are both being chronically dosed. No initial dosage adjustment of paroxetine is considered necessary when coadministered with phenobarbital; any subsequent adjustment should be guided by clinical effect.

Phenytoin: When a single oral 30 mg dose of paroxetine was administered at phenytoin steady-state (300 mg once daily for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 50% and 35%, respectively) compared to paroxetine administered alone. In a separate study, when a single oral 300 mg dose of phenytoin was administered at paroxetine steady-state (30 mg once daily for 14 days), phenytoin AUC was slightly reduced (12% on average) compared to phenytoin administered alone. Since both drugs exhibit nonlinear pharmacokinetics, the above studies may not address the case where the 2 drugs are both being chronically dosed. No initial dosage adjustments are considered necessary when these drugs are coadministered; any subsequent adjustments should be guided by clinical effect (see ADVERSE REACTIONS: Postmarketing Reports).

Drugs Metabolized by CYP2D6: Many drugs, including most drugs effective in the treatment of major depressive disorder (paroxetine, other SSRIs and many tricyclics), are metabolized by the cytochrome P_{450} isozyme CYP2D6. Like other agents that are metabolized by CYP2D6, paroxetine may significantly inhibit the activity of this isozyme. In most patients (> 90%), this CYP2D6 isozyme is saturated early during dosing with paroxetine. In 1 study, daily dosing of paroxetine (20 mg once daily) under steady-state conditions increased single dose desipramine (100 mg) C_{max}, AUC, and $T_{1/2}$ by an average of approximately 2-, 5-, and 3-fold, respectively. Concomitant use of paroxetine with risperidone, a CYP2D6 substrate has also been evaluated. In 1 study, daily dosing of paroxetine 20 mg in patients stabilized on risperidone (4 to 8 mg/day) increased mean plasma concentrations of risperidone approximately 4-fold, decreased 9-hydroxyrisperidone concentrations approximately 10%, and increased concentrations of the active moiety (the sum of risperidone plus 9-hydroxyrisperidone) approximately 1.4-fold. The effect of paroxetine on the pharmacokinetics of atomoxetine has been evaluated when both drugs were at steady-state. In healthy volunteers who were extensive metabolizers of CYP2D6, paroxetine 20 mg daily was given in combination with 20 mg atomoxetine every 12 hours. This resulted in increases in steady-state atomoxetine AUC values that were 6- to 8-fold greater and in atomoxetine C_{max} values that were 3- to 4-fold greater than when atomoxetine was given alone. Dosage adjustment of atomoxetine may be necessary and it is recommended that atomoxetine be initiated at a reduced dose when it is given with paroxetine.

Concomitant use of paroxetine with other drugs metabolized by cytochrome CYP2D6 has not been formally studied but may require lower doses than usually prescribed for either paroxetine or the other drug.

Therefore, coadministration of paroxetine with other drugs that are metabolized by this isozyme, including certain drugs effective in the treatment of major depressive disorder (e.g., nortriptyline, amitriptyline, imipramine, desipramine, and fluoxetine), phenothiazines, risperidone, and Type 1C antiarrhythmics (e.g., propafenone, flecainide, and encainide), or that inhibit this enzyme (e.g., quinidine), should be approached with caution.

However, due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, paroxetine and thioridazine should not be coadministered (see CONTRAINDICATIONS and WARNINGS).

Tamoxifen is a pro-drug requiring metabolic activation by CYP2D6. Inhibition of CYP2D6 by paroxetine may lead to reduced plasma concentrations of an active metabolite (endoxifen) and hence reduced efficacy of tamoxifen (see PRECAUTIONS).

At steady-state, when the CYP2D6 pathway is essentially saturated, paroxetine clearance is governed by alternative P_{450} isozymes that, unlike CYP2D6, show no evidence of saturation (see PRECAUTIONS: *Tricyclic Antidepressants [TCAs]).*

Drugs Metabolized by Cytochrome CYP3A4: An in vivo interaction study involving the coadministration under steady-state conditions of paroxetine and terfenadine, a substrate for cytochrome CYP3A4, revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, in vitro studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam, and cyclosporine. Based on the assumption that the relationship between paroxetine's in vitro K_i and its lack of effect on terfenadine's in vivo clearance predicts its effect on other CYP3A4 substrates, paroxetine's extent of inhibition of CYP3A4 activity is not likely to be of clinical significance.

Tricyclic Antidepressants (TCAs): Caution is indicated in the coadministration of tricyclic antidepressants (TCAs) with paroxetine, because paroxetine may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is coadministered with paroxetine (see PRECAUTIONS: *Drugs Metabolized by Cytochrome CYP2D6*).

Drugs Highly Bound to Plasma Protein: Because paroxetine is highly bound to plasma protein, administration of paroxetine to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events. Conversely, adverse effects could result from displacement of paroxetine by other highly bound drugs.

Drugs That Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin): 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 this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when paroxetine is initiated or discontinued.

Alcohol: Although paroxetine does not increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking paroxetine.

Lithium: A multiple-dose study has shown that there is no pharmacokinetic interaction between paroxetine and lithium carbonate. However, due to the potential for serotonin syndrome, caution is advised when paroxetine is coadministered with lithium.

Digoxin: The steady-state pharmacokinetics of paroxetine was not altered when administered with digoxin at steady-state. Mean digoxin AUC at steady-state decreased by 15% in the presence of paroxetine. Since there is little clinical experience, the concurrent administration of paroxetine and digoxin should be undertaken with caution.

Diazepam: Under steady-state conditions, diazepam does not appear to affect paroxetine kinetics. The effects of paroxetine on diazepam were not evaluated.

Procyclidine: Daily oral dosing of paroxetine tablets (30 mg once daily) increased steady-state AUC_{0-24}, C_{max}, and C_{min} values of procyclidine (5 mg oral once daily) by 35%, 37%, and 67%, respectively, compared to procyclidine alone at steady-state. If anticholinergic effects are seen, the dose of procyclidine should be reduced.

Beta-Blockers: In a study where propranolol (80 mg twice daily) was dosed orally for 18 days, the established steady-state plasma concentrations of propranolol were unaltered during coadministration with paroxetine (30 mg once daily) for the final 10 days. The effects of propranolol on paroxetine have not been evaluated (see ADVERSE REACTIONS: Postmarketing Reports).

Theophylline: Reports of elevated theophylline levels associated with treatment with paroxetine have been reported. While this interaction has not been formally studied, it is recommended that theophylline levels be monitored when these drugs are concurrently administered.

Fosamprenavir/Ritonavir: Co-administration of fosamprenavir/ritonavir with paroxetine significantly decreased plasma levels of paroxetine. Any dose adjustment should be guided by clinical effect (tolerability and efficacy).

Electroconvulsive Therapy (ECT): There are no clinical studies of the combined use of ECT and paroxetine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: ***Carcinogenesis:*** Two-year carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to 2.4 (mouse) and 3.9 (rat) times the MRHD for major depressive disorder, social anxiety disorder, and GAD on a mg/m² basis. Because the MRHD for major depressive disorder is slightly less than that for OCD (50 mg versus 60 mg), the doses used in these carcinogenicity studies were only 2.0 (mouse) and 3.2 (rat) times the MRHD for OCD. There was a significantly greater number of male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50, and 4/50 for control, low-, middle-, and high-dose groups, respectively) and a significantly increased linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The relevance of these findings to humans is unknown.

Mutagenesis: Paroxetine produced no genotoxic effects in a battery of 5 in vitro and 2 in vivo assays that included the following: Bacterial mutation assay, mouse lymphoma mutation assay, unscheduled DNA synthesis assay, and tests for cytogenetic aberrations in vivo in mouse bone marrow and in vitro in human lymphocytes and in a dominant lethal test in rats.

Impairment of Fertility: Some clinical studies have shown that SSRIs (including paroxetine) may affect sperm quality during SSRI treatment, which may affect fertility in some men.

A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of 15 mg/kg/day, which is 2.9 times the MRHD for major depressive disorder, social anxiety disorder, and GAD or 2.4 times the MRHD for OCD on a mg/m² basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks. These lesions consisted of vacuolation of epididymal tubular epithelium at 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis at 25 mg/kg/day (9.8 and 4.9 times the MRHD for major depressive disorder, social anxiety disorder, and GAD; 8.2 and 4.1 times the MRHD for OCD and PD on a mg/m² basis).

Medication Guide
Paroxetine Tablets, USP
(pa rox' e teen)

Read the Medication Guide that comes with paroxetine tablets before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment. Talk with your healthcare provider if there is something you do not understand or want to learn more about.

What is the most important information I should know about paroxetine tablets?

Paroxetine tablets and other antidepressant medicines may cause serious side effects, including:

1. **Suicidal thoughts or actions:**
   - **Paroxetine tablets and other antidepressant medicines may increase suicidal thoughts or actions** in some children, teenagers, or young adults within the **first few months of treatment or when the dose is changed.**
   - Depression or other serious mental illnesses are the most important causes of suicidal thoughts or actions.
   - Watch for these changes and call your healthcare provider right away if you notice:
     - New or sudden changes in mood, behavior, actions, thoughts, or feelings, especially if severe.
     - Pay particular attention to such changes when paroxetine tablets are started or when the dose is changed.

   Keep all follow-up visits with your healthcare provider and call between visits if you are worried about symptoms.

   Call your healthcare provider right away if you have any of the following symptoms, or call 911 if an emergency, especially if they are new, worse, or worry you:
   - attempts to commit suicide
   - acting on dangerous impulses
   - acting aggressive or violent
   - thoughts about suicide or dying
   - new or worse depression
   - new or worse anxiety or panic attacks
   - feeling agitated, restless, angry, or irritable
   - trouble sleeping
   - an increase in activity or talking more than what is normal for you
   - other unusual changes in behavior or mood

   Call your healthcare provider right away if you have any of the following symptoms, or call 911 if an emergency. Paroxetine tablets may be associated with these serious side effects:
2. **Serotonin Syndrome or Neuroleptic Malignant Syndrome-like reactions. This condition can be life-threatening and may include:**
   - agitation, hallucinations, coma, or other changes in mental status
   - coordination problems or muscle twitching (overactive reflexes)
   - racing heartbeat, high or low blood pressure
   - sweating or fever
   - nausea, vomiting, or diarrhea
   - muscle rigidity
3. **Visual problems**
   - eye pain
   - changes in vision
   - swelling or redness in or around the eye

   Only some people are at risk for these problems. You may want to undergo an eye examination to see if you are at risk and receive preventative treatment if you are.
4. **Severe allergic reactions:**
   - trouble breathing
   - swelling of the face, tongue, eyes, or mouth
   - rash, itchy welts (hives), or blisters, alone or with fever or joint pain
5. **Abnormal bleeding:** Paroxetine tablets and other antidepressant medicines may increase your risk of bleeding or bruising, especially if you take the blood thinner warfarin (Coumadin®*, Jantoven®*), a non-steroidal anti-inflammatory drug (NSAIDs, like ibuprofen or naproxen), or aspirin.
6. **Seizures or convulsions**
7. **Manic episodes:**
   - greatly increased energy
   - severe trouble sleeping
   - racing thoughts
   - reckless behavior
   - unusually grand ideas
   - excessive happiness or irritability
   - talking more or faster than usual
8. **Changes in appetite or weight.** Children and adolescents should have height and weight monitored during treatment.
9. **Low salt (sodium) levels in the blood.** Elderly people may be at greater risk for this. Symptoms may include:
   - headache
   - weakness or feeling unsteady
   - confusion, problems concentrating or thinking, or memory problems

Do not stop paroxetine tablets without first talking to your healthcare provider. Stopping paroxetine tablets too quickly may cause serious symptoms including:

- anxiety, irritability, high or low mood, feeling restless, or changes in sleep habits
- headache, sweating, nausea, dizziness
- electric shock-like sensations, shaking, confusion

What are paroxetine tablets?

Paroxetine tablets are prescription medicine used to treat depression. It is important to talk with your healthcare provider about the risks of treating depression and also the risks of not treating it. You should discuss all treatment choices with your healthcare provider. Paroxetine tablets are also used to treat:

- Major Depressive Disorder (MDD)
- Obsessive Compulsive Disorder (OCD)
- Panic Disorder
- Social Anxiety Disorder
- Generalized Anxiety Disorder (GAD)

Talk to your healthcare provider if you do not think that your condition is getting better with treatment using paroxetine tablets.

Who should not take paroxetine tablets?

Do not take paroxetine tablets if you:

- are allergic to paroxetine or any of the ingredients in paroxetine tablets. See the end of this Medication Guide for a complete list of ingredients in paroxetine tablets.
- take a monoamine oxidase inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid.
  - Do not take an MAOI within 2 weeks of stopping paroxetine tablets unless directed to do so by your physician.
  - Do not start paroxetine tablets if you stopped taking an MAOI in the last 2 weeks unless directed to do so by your physician.
  - **People who take paroxetine tablets close in time to an MAOI may have serious or even life-threatening side effects. Get medical help right away if you have any of these symptoms:**
    - high fever
    - uncontrolled muscle spasms
    - stiff muscles
    - rapid changes in heart rate or blood pressure
    - confusion
    - loss of consciousness (pass out)
- **take MELLARIL®* (thioridazine). Do not take MELLARIL®* together with paroxetine tablets because this can cause serious heart rhythm problems or sudden death.**
- **take the antipsychotic medicine pimozide (ORAP®*) because this can cause serious heart problems.**

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Reason for Artwork: New	JUBILANT GENERICS	Dimension: 880 x 500 mm
Item Code: 7524000687		Superseded Item Code: NA
Substrate: 32 GSM Bible paper with folding size- 43 x 43 mm		
Site Packaging Development Sign and Date	Production Sign and Date	QA Sign and Date

7524000687

Neutral Code No.UK/Drugs/58/UA/2007

Pregnancy: Pregnancy Category D. See WARNINGS: Usage in Pregnancy: *Teratogenic Effects* and *Nonteratogenic Effects*.

Labor and Delivery: The effect of paroxetine on labor and delivery in humans is unknown.

Nursing Mothers: Like many other drugs, paroxetine is secreted in human milk, and caution should be exercised when paroxetine is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS: Clinical Worsening and Suicide Risk). Three placebo-controlled trials in 752 pediatric patients with MDD have been conducted with paroxetine, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of paroxetine in a child or adolescent must balance the potential risks with the clinical need. Decreased appetite and weight loss have been observed in association with the use of SSRIs. Consequently, regular monitoring of weight and growth should be performed in children and adolescents treated with an SSRI such as paroxetine.

In placebo-controlled clinical trials conducted with pediatric patients, the following adverse events were reported in at least 2% of pediatric patients treated with paroxetine and occurred at a rate at least twice that for pediatric patients receiving placebo: emotional lability (including self-harm, suicidal thoughts, attempted suicide, crying, and mood fluctuations), hostility, decreased appetite, tremor, sweating, hyperkinesia, and agitation.

Events reported upon discontinuation of treatment with paroxetine in the pediatric clinical trials that included a taper phase regimen, which occurred in at least 2% of patients who received paroxetine and which occurred at a rate at least twice that of placebo, were: emotional lability (including suicidal ideation, suicide attempt, mood changes, and tearfulness), nervousness, dizziness, nausea, and abdominal pain (see DOSAGE AND ADMINISTRATION: Discontinuation of Treatment With Paroxetine).

Geriatric Use: SSRIs and SNRIs, including paroxetine, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event (see PRECAUTIONS: Hyponatremia).

In worldwide premarketing clinical trials with paroxetine, 17% of patients treated with paroxetine (approximately 700) were 65 years of age or older. Pharmacokinetic studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended; there were, however, no overall differences in the adverse event profile between elderly and younger patients, and effectiveness was similar in younger and older patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Associated With Discontinuation of Treatment: Twenty percent (1,199/6,145) of patients treated with paroxetine in worldwide clinical trials in major depressive disorder and 16.1% (84/522), 11.8% (64/542), 9.4% (44/469), and 10.7% (79/735) of patients treated with paroxetine in worldwide trials in social anxiety disorder, OCD, panic disorder, and GAD, respectively, discontinued treatment due to an adverse event. The most common events (≥ 1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate approximately twice or greater for paroxetine compared to placebo) included the following:

	Major Depressive Disorder		OCD		Panic Disorder		Social Anxiety Disorder		Generalized Anxiety Disorder	
	Paroxetine	Placebo	Paroxetine	Placebo	Paroxetine	Placebo	Paroxetine	Placebo	Paroxetine	Placebo
CNS										
Somnolence	2.3%	0.7%	-		1.9%	0.3%	3.4%	0.3%	2.0%	0.2%
Insomnia	-	-	1.7%	0.0%	1.3%	0.3%	3.1%	0.0%		
Agitation	1.1%	0.5%	-							
Tremor	1.1%	0.3%	-				1.7%	0.0%		
Anxiety	-	-	-				1.1%	0.0%		
Dizziness	-	-	1.5%	0.0%			1.9%	0.0%	1.0%	0.2%
Gastrointestinal										
Constipation	-		1.1%	0.0%						
Nausea	3.2%	1.1%	1.9%	0.0%	3.2%	1.2%	4.0%	0.3%	2.0%	0.2%
Diarrhea	1.0%	0.3%	-							
Dry mouth	1.0%	0.3%	-							
Vomiting	1.0%	0.3%	-				1.0%	0.0%		
Flatulence							1.0%	0.3%		
Other										
Asthenia	1.6%	0.4%	1.9%	0.4%			2.5%	0.6%	1.8%	0.2%
Abnormal Ejaculation[a]	1.6%	0.0%	2.1%	0.0%			4.9%	0.6%	2.5%	0.5%
Sweating	1.0%	0.3%	-				1.1%	0.0%	1.1%	0.2%
Impotence[a]	-		1.5%	0.0%						
Libido Decreased							1.0%	0.0%		

Where numbers are not provided the incidence of the adverse events in patients treated with paroxetine was not >1% or was not greater than or equal to 2 times the incidence of placebo.

a Incidence corrected for gender.

Commonly Observed Adverse Events: ***Major Depressive Disorder:*** The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine at least twice that for placebo, derived from Table 2) were: Asthenia, sweating, nausea, decreased appetite, somnolence, dizziness, insomnia, tremor, nervousness, ejaculatory disturbance, and other male genital disorders.

Obsessive Compulsive Disorder: The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine at least twice that of placebo, derived from Table 3) were: Nausea, dry mouth, decreased appetite, constipation, dizziness, somnolence, tremor, sweating, impotence, and abnormal ejaculation.

Panic Disorder: The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine at least twice that for placebo, derived from Table 3) were: Asthenia, sweating, decreased appetite, libido decreased, tremor, abnormal ejaculation, female genital disorders, and impotence.

Social Anxiety Disorder: The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine at least twice that for placebo, derived from Table 3) were: Sweating, nausea, dry mouth, constipation, decreased appetite, somnolence, tremor, libido decreased, yawn, abnormal ejaculation, female genital disorders, and impotence.

Generalized Anxiety Disorder: The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine at least twice that for placebo, derived from Table 4) were: Asthenia, infection, constipation, decreased appetite, dry mouth, nausea, libido decreased, somnolence, tremor, sweating, and abnormal ejaculation.

Incidence in Controlled Clinical Trials: The prescriber should be aware that the figures in the tables following cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that 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 nondrug factors to the side effect incidence rate in the populations studied.

Major Depressive Disorder: Table 2 enumerates adverse events that occurred at an incidence of 1% or more among paroxetine-treated patients who participated in short-term (6-week) placebo-controlled trials in which patients were dosed in a range of 20 mg to 50 mg/day. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

Table 2. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder[a]

Body System	Preferred Term	Paroxetine (n = 421)	Placebo (n = 421)
Body as a Whole	Headache	18%	17%
	Asthenia	15%	6%
Cardiovascular	Palpitation	3%	1%
	Vasodilation	3%	1%
Dermatologic	Sweating	11%	2%
	Rash	2%	1%
Gastrointestinal	Nausea	26%	9%
	Dry Mouth	18%	12%
	Constipation	14%	9%
	Diarrhea	12%	8%
	Decreased Appetite	6%	2%
	Flatulence	4%	2%
	Oropharynx Disorder[b]	2%	0%
	Dyspepsia	2%	1%
Musculoskeletal	Myopathy	2%	1%
	Myalgia	2%	1%
	Myasthenia	1%	0%
Nervous System	Somnolence	23%	9%
	Dizziness	13%	6%
	Insomnia	13%	6%
	Tremor	8%	2%
	Nervousness	5%	3%
	Anxiety	5%	3%
	Paresthesia	4%	2%
	Libido Decreased	3%	0%
	Drugged Feeling	2%	1%
	Confusion	1%	0%
Respiration	Yawn	4%	0%
Special Senses	Blurred Vision	4%	1%
	Taste Perversion	2%	0%
Urogenital System	Ejaculatory Disturbance[c,d]	13%	0%
	Other Male Genital Disorders[c,e]	10%	0%
	Urinary Frequency	3%	1%
	Urination Disorder[f]	3%	0%
	Female Genital Disorders[c,g]	2%	0%

a Events reported by at least 1% of patients treated with paroxetine are included, except the following events which had an incidence on placebo ≥ paroxetine: Abdominal pain, agitation, back pain, chest pain, CNS stimulation, fever, increased appetite, myoclonus, pharyngitis, postural hypotension, respiratory disorder (includes mostly "cold symptoms" or "URI"), trauma, and vomiting.

b Includes mostly "lump in throat" and "tightness in throat".

c Percentage corrected for gender.

d Mostly "ejaculatory delay".

e Includes "anorgasmia," "erectile difficulties," "delayed ejaculation/orgasm," and "sexual dysfunction," and "impotence".

f Includes mostly "difficulty with micturition" and "urinary hesitancy".

g Includes mostly "anorgasmia" and "difficulty reaching climax/orgasm".

Obsessive Compulsive Disorder, Panic Disorder, and Social Anxiety Disorder: Table 3 enumerates adverse events that occurred at a frequency of 2% or more among OCD patients on paroxetine who participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20 mg to 60 mg/day or among patients with panic disorder on paroxetine who participated in placebo-controlled trials of 10- to 12 - weeks duration in which patients were dosed in a range of 10 mg to 60 mg/day or among patients with social anxiety disorder on paroxetine who participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20 mg to 50 mg/day.

Table 3. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Obsessive Compulsive Disorder, Panic Disorder, and Social Anxiety Disorder[a]

Body System	Preferred Term	Obsessive Compulsive Disorder: Paroxetine (n = 542)	Obsessive Compulsive Disorder: Placebo (n = 265)	Panic Disorder: Paroxetine (n = 469)	Panic Disorder: Placebo (n = 324)	Social Anxiety Disorder: Paroxetine (n = 425)	Social Anxiety Disorder: Placebo (n = 339)
Body as a Whole	Asthenia	22%	14%	14%	5%	22%	14%
	Abdominal Pain	-	-	4%	3%	-	-
	Chest Pain	3%	2%	-	-	-	-
	Back Pain	-	-	3%	2%	-	-
	Chills	2%	1%	2%	1%	-	-
	Trauma	-	-	-	-	3%	1%
Cardiovascular	Vasodilation	4%	1%	-	-	-	-
	Palpitation	2%	0%	-	-	-	-
Dermatologic	Sweating	9%	3%	14%	6%	9%	2%
	Rash	3%	2%	-	-	-	-
Gastrointestinal	Nausea	23%	10%	23%	17%	25%	7%
	Dry Mouth	18%	9%	18%	11%	9%	3%
	Constipation	16%	6%	8%	5%	5%	2%
	Diarrhea	10%	10%	12%	7%	9%	6%
	Decreased Appetite	9%	3%	7%	3%	8%	2%
	Dyspepsia	-	-	-	-	4%	2%
	Flatulence	-	-	-	-	4%	2%
	Increased Appetite	4%	3%	2%	1%	-	-
	Vomiting	-	-	-	-	2%	1%
Musculoskeletal	Myalgia	-	-	-	-	4%	3%
Nervous System	Insomnia	24%	13%	18%	10%	21%	16%
	Somnolence	24%	7%	19%	11%	22%	5%
	Dizziness	12%	6%	14%	10%	11%	7%
	Tremor	11%	1%	9%	1%	9%	1%
	Nervousness	9%	8%	-	-	8%	7%
	Libido Decreased	7%	4%	9%	1%	12%	1%
	Agitation	-	-	5%	4%	3%	1%
	Anxiety	-	-	5%	4%	5%	4%
	Abnormal Dreams	4%	1%	-	-	-	-
	Concentration Impaired	3%	2%	-	-	4%	1%
	Depersonalization	3%	0%	-	-	-	-
	Myoclonus	3%	0%	3%	2%	2%	1%
	Amnesia	2%	1%	-	-	-	-
Respiratory System	Rhinitis	-	-	3%	0%	-	-
	Pharyngitis	-	-	-	-	4%	2%
	Yawn	-	-	-	-	5%	1%
Special Senses	Abnormal Vision	4%	2%	-	-	4%	1%
	Taste Perversion	2%	0%	-	-	-	-
Urogenital System	Abnormal Ejaculation[b]	23%	1%	21%	1%	28%	1%
	Dysmenorrhea	-	-	-	-	5%	4%
	Female Genital Disorder[b]	3%	0%	9%	1%	9%	1%
	Impotence[b]	8%	1%	5%	0%	5%	1%
	Urinary Frequency	3%	1%	2%	0%	-	-
	Urination Impaired	3%	0%	-	-	-	-
	Urinary Tract Infection	2%	1%	2%	1%	-	-

a Events reported by at least 2% of OCD, panic disorder, and social anxiety disorder in patients treated with paroxetine are included, except the following events which had an incidence on placebo ≥ paroxetine: [OCD]: Abdominal pain, agitation, anxiety, back pain, cough increased, depression, headache, hyperkinesia, infection, paresthesia, pharyngitis, respiratory disorder, rhinitis, and sinusitis. [panic disorder]: Abnormal dreams, abnormal vision, chest pain, cough increased, depersonalization, depression, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, myalgia, nervousness, palpitation, paresthesia, pharyngitis, rash, respiratory disorder, sinusitis, taste perversion, trauma, urination impaired, and vasodilation. [social anxiety disorder]: Abdominal pain, depression, headache, infection, respiratory disorder, and sinusitis.

b Percentage corrected for gender.

Generalized Anxiety Disorder: Table 4 enumerates adverse events that occurred at a frequency of 2% or more among GAD patients on paroxetine who participated in placebo-controlled trials of 8-weeks duration in which patients were dosed in a range of 10 mg/day to 50 mg/day.

Table 4. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder[a]

Body System	Preferred Term	Generalized Anxiety Disorder: Paroxetine (n = 735)	Generalized Anxiety Disorder: Placebo (n = 529)
Body as a Whole	Asthenia	14%	6%
	Headache	17%	14%
	Infection	6%	3%
	Abdominal Pain		
	Trauma		
Cardiovascular	Vasodilation	3%	1%
Dermatologic	Sweating	6%	2%
Gastrointestinal	Nausea	20%	5%
	Dry Mouth	11%	5%
	Constipation	10%	2%
	Diarrhea	9%	7%
	Decreased Appetite	5%	1%
	Vomiting	3%	2%
	Dyspepsia	-	-
Nervous System	Insomnia	11%	8%
	Somnolence	15%	5%
	Dizziness	6%	5%
	Tremor	5%	1%
	Nervousness	4%	3%
	Libido Decreased	9%	2%
	Abnormal Dreams		
Respiratory System	Respiratory Disorder	7%	5%
	Sinusitis	4%	3%
	Yawn	4%	-
Special Senses	Abnormal Vision	2%	1%
Urogenital System	Abnormal Ejaculation[b]	25%	2%
	Female Genital Disorder[b]	4%	1%
	Impotence[b]	4%	3%

a Events reported by at least 2% of GAD in patients treated with paroxetine are included, except the following events which had an incidence on placebo ≥ paroxetine [GAD]: Abdominal pain, back pain, trauma, dyspepsia, myalgia, and pharyngitis.

b Percentage corrected for gender.

Dose Dependency of Adverse Events: A comparison of adverse event rates in a fixed-dose study comparing 10, 20, 30, and 40 mg/day of paroxetine with placebo in the treatment of major depressive disorder revealed a clear dose dependency for some of the more common adverse events associated with use of paroxetine, as shown in Table 5:

Table 5. Treatment-Emergent Adverse Experience Incidence in a Dose-Comparison Trial in the Treatment of Major Depressive Disorder[a]

Body System/Preferred Term	Placebo n = 51	Paroxetine 10 mg n = 102	Paroxetine 20 mg n = 104	Paroxetine 30 mg n = 101	Paroxetine 40 mg n = 102
Body as a Whole					
Asthenia	0.0%	2.9%	10.6%	13.9%	12.7%
Dermatology					
Sweating	2.0%	1.0%	6.7%	8.9%	11.8%
Gastrointestinal					
Constipation	5.9%	4.9%	7.7%	9.9%	12.7%
Decreased Appetite	2.0%	2.0%	5.8%	4.0%	4.9%
Diarrhea	7.8%	9.8%	19.2%	7.9%	14.7%
Dry Mouth	2.0%	10.8%	18.3%	15.8%	20.6%
Nausea	13.7%	14.7%	26.9%	34.7%	36.3%
Nervous System					
Anxiety	0.0%	2.0%	5.8%	5.9%	5.9%
Dizziness	3.9%	6.9%	6.7%	8.9%	12.7%
Nervousness	0.0%	5.9%	5.8%	4.0%	2.9%
Paresthesia	0.0%	2.9%	1.0%	5.0%	5.9%
Somnolence	7.8%	12.7%	18.3%	20.8%	21.6%
Tremor	0.0%	0.0%	7.7%	7.9%	14.7%
Special Senses					
Blurred Vision	2.0%	2.9%	2.9%	2.0%	7.8%
Urogenital System					
Abnormal Ejaculation	0.0%	5.8%	6.5%	10.6%	13.0%
Impotence	0.0%	1.9%	4.3%	6.4%	1.9%
Male Genital Disorders	0.0%	3.8%	8.7%	6.4%	3.7%

a Rule for including adverse events in table: Incidence at least 5% for 1 of paroxetine groups and ≥ twice the placebo incidence for at least 1 paroxetine group.

In a fixed-dose study comparing placebo and 20, 40, and 60 mg of paroxetine in the treatment of OCD, there was no clear relationship between adverse events and the dose of paroxetine to which patients were assigned. No new adverse events were observed in the group treated with 60 mg of paroxetine compared to any of the other treatment groups.

In a fixed-dose study comparing placebo and 10, 20, and 40 mg of paroxetine in the treatment of panic disorder, there was no clear relationship between adverse events and the dose of paroxetine to which patients were assigned, except for asthenia, dry mouth, anxiety, libido decreased, tremor, and abnormal ejaculation. In flexible-dose studies, no new adverse events were observed in patients receiving 60 mg of paroxetine compared to any of the other treatment groups.

In a fixed-dose study comparing placebo and 20, 40, and 60 mg of paroxetine in the treatment of social anxiety disorder, for most of the adverse events, there was no clear relationship between adverse events and the dose of paroxetine to which patients were assigned.

In a fixed-dose study comparing placebo and 20 and 40 mg of paroxetine in the treatment of generalized anxiety disorder, for most of the adverse events, there was no clear relationship between adverse events and the dose of paroxetine to which patients were assigned, except for the following adverse events: Asthenia, constipation, and abnormal ejaculation.

Adaptation to Certain Adverse Events: Over a 4-to 6-week period, there was evidence of adaptation to some adverse events with continued therapy (e.g., nausea and dizziness), but less to other effects (e.g., dry mouth, somnolence, and asthenia).

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 selective serotonin reuptake inhibitors (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.

In placebo-controlled clinical trials involving more than 3,200 patients, the ranges for the reported incidence of sexual side effects in males and females with major depressive disorder, OCD, panic disorder, social anxiety disorder, and GAD are displayed in Table 6.

Table 6. Incidence of Sexual Adverse Events in Controlled Clinical Trials

	Paroxetine	Placebo
n (males)	**1446**	**1042**
Decreased Libido	6-15%	0-5%
Ejaculatory Disturbance	13-28%	0-2%
Impotence	2-9%	0-3%
n (females)	**1822**	**1340**
Decreased Libido	0-9%	0-2%
Orgasmic Disturbance	2-9%	0-1%

There are no adequate and well-controlled studies examining sexual dysfunction with paroxetine treatment.

Paroxetine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae.

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.

Weight and Vital Sign Changes: Significant weight loss may be an undesirable result of treatment with paroxetine for some patients but, on average, patients in controlled trials had minimal (about 1 pound) weight loss versus smaller changes on placebo and active control. No significant changes in vital signs (systolic and diastolic blood pressure, pulse and temperature) were observed in patients treated with paroxetine in controlled clinical trials.

ECG Changes: In an analysis of ECGs obtained in 682 patients treated with paroxetine and 415 patients treated with placebo in controlled clinical trials, no clinically significant changes were seen in the ECGs of either group.

Liver Function Tests: In placebo-controlled clinical trials, patients treated with paroxetine exhibited abnormal values on liver function tests at no greater rate than that seen in placebo-treated patients. In particular, the paroxetine-versus-placebo comparisons for alkaline phosphatase, SGOT, SGPT, and bilirubin revealed no differences in the percentage of patients with marked abnormalities.

Hallucinations: In pooled clinical trials of immediate-release paroxetine hydrochloride, hallucinations were observed in 22 of 9089 patients receiving drug and 4 of 3187 patients receiving placebo.

Other Events Observed During the Premarketing Evaluation of Paroxetine: During its premarketing assessment in major depressive disorder, multiple doses of paroxetine were administered to 6,145 patients in phase 2 and 3 studies. The conditions and duration of exposure to paroxetine varied greatly and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose, and titration studies. During premarketing clinical trials in OCD, panic disorder, social anxiety disorder, and generalized anxiety disorder, 542, 469, 522, and 735 patients, respectively, received multiple doses of paroxetine. Untoward events associated with this exposure were 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 untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 9,089 patients exposed to multiple doses of paroxetine who experienced an event of the type cited on at least 1 occasion while receiving paroxetine. All reported events are included except those already listed in Tables 2 to 5, those reported in terms so general as to be uninformative and those events where a drug cause was remote. It is important to emphasize that although the events reported occurred during treatment with paroxetine, 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 1 or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients. Events of major clinical importance are also described in the PRECAUTIONS section.

Body as a Whole: *Infrequent:* Allergic reaction, chills, face edema, malaise, neck pain; *rare:* Adrenergic syndrome, cellulitis, moniliasis, neck rigidity, pelvic pain, peritonitis, sepsis, ulcer.

Cardiovascular System: *Frequent:* Hypertension, tachycardia; *infrequent:* Bradycardia, hematoma, hypotension, migraine, postural hypotension, syncope; *rare:* Angina pectoris, arrhythmia nodal, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, heart block, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, varicose vein, vascular headache, ventricular extrasystoles.

Digestive System: *Infrequent:* Bruxism, colitis, dysphagia, eructation, gastritis, gastroenteritis, gingivitis, glossitis, increased salivation, liver function tests abnormal, rectal hemorrhage, ulcerative stomatitis; *rare:* Aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, intestinal obstruction, jaundice, melena, mouth ulceration, peptic ulcer, salivary gland enlargement, sialadenitis, stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries.

Endocrine System: *Rare:* Diabetes mellitus, goiter, hyperthyroidism, hypothyroidism, thyroiditis.

Hemic and Lymphatic Systems: *Infrequent:* Anemia, leukopenia, lymphadenopathy, purpura; *rare:* Abnormal erythrocytes, basophilia, bleeding time increased, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia, thrombocytopenia.

Metabolic and Nutritional: *Frequent:* Weight gain; *infrequent:* Edema, peripheral edema, SGOT increased, SGPT increased, thirst, weight loss; *rare:* Alkaline phosphatase increased, bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperglycemia, hyperkalemia, hyperphosphatemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased.

Musculoskeletal System: *Frequent:* Arthralgia; *infrequent:* Arthritis, arthrosis; *rare:* Bursitis, myositis, osteoporosis, generalized spasm, tenosynovitis, tetany.

Nervous System: *Frequent:* Emotional lability, vertigo; *infrequent:* Abnormal thinking, alcohol abuse, ataxia, dystonia, dyskinesia, euphoria, hallucinations, hostility, hypertonia, hypesthesia, hypokinesia, incoordination, lack of emotion, libido increased, manic reaction, neurosis, paralysis, paranoid reaction; *rare:* Abnormal gait, akinesia, antisocial reaction, aphasia, choreoathetosis, circumoral paresthesias, convulsion, delirium, delusions, diplopia, drug dependence, dysarthria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, hysteria, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, peripheral neuritis, psychotic depression, psychosis, reflexes decreased, reflexes increased, stupor, torticollis, trismus, withdrawal syndrome.

Respiratory System: *Infrequent:* Asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu; *rare:* Emphysema, hemoptysis, hiccups, lung fibrosis, pulmonary edema, sputum increased, stridor, voice alteration.

Skin and Appendages: *Frequent:* Pruritus; *infrequent:* Acne, alopecia, contact dermatitis, dry skin, ecchymosis, eczema, herpes simplex, photosensitivity, urticaria; *rare:* Angioedema, erythema nodosum, erythema multiforme, exfoliative dermatitis, fungal dermatitis, furunculosis; herpes zoster, hirsutism, maculopapular rash, seborrhea, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash.

Special Senses: *Frequent:* Tinnitus; *infrequent:* Abnormality of accommodation, conjunctivitis, ear pain, eye pain, keratoconjunctivitis, mydriasis, otitis media; *rare:* Amblyopia, anisocoria, blepharitis, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, night blindness, otitis externa, parosmia, photophobia, ptosis, retinal hemorrhage, taste loss, visual field defect.

Urogenital System: *Infrequent:* Amenorrhea, breast pain, cystitis, dysuria, hematuria, menorrhagia, nocturia, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginitis; *rare:* Abortion, breast atrophy, breast enlargement, endometrial disorder, epididymitis, female lactation, fibrocystic breast, kidney calculus, kidney pain, leukorrhea, mastitis, metrorrhagia, nephritis, oliguria, salpingitis, urethritis, urinary casts, uterine spasm, urolith, vaginal hemorrhage, vaginal moniliasis.

Postmarketing Reports: Voluntary reports of adverse events in patients taking paroxetine that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide; tremor and trismus; status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, restless legs syndrome (RLS), ventricular fibrillation, ventricular tachycardia (including torsades de pointes), thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura), and premature births in pregnant women. There has been a case report of an elevated phenytoin level after 4 weeks of paroxetine and phenytoin coadministration. There has been a case report of severe hypotension when paroxetine was added to chronic metoprolol treatment.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: Paroxetine is not a controlled substance.

Physical and Psychologic Dependence: Paroxetine has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, 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, patients should be evaluated carefully for history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of paroxetine (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience: Since the introduction of paroxetine in the United States, 342 spontaneous cases of deliberate or accidental overdosage during paroxetine treatment have been reported worldwide (circa 1999). These include overdoses with paroxetine alone and in combination with other substances. Of these, 48 cases were fatal and of the fatalities, 17 appeared to involve paroxetine alone. Eight fatal cases that documented the amount of paroxetine ingested were generally confounded by the ingestion of other drugs or alcohol or the presence of significant comorbid conditions. Of 145 non-fatal cases with known outcome, most recovered without sequelae. The largest known ingestion involved 2,000 mg of paroxetine (33 times the maximum recommended daily dose) in a patient who recovered.

Commonly reported adverse events associated with paroxetine overdosage include somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other notable signs and symptoms observed with overdoses involving paroxetine (alone or with other substances) include mydriasis, convulsions (including status epilepticus), ventricular dysrhythmias (including torsades de pointes), hypertension, aggressive reactions, syncope, hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

Overdosage Management: No specific antidotes for paroxetine are known. Treatment should consist of those general measures employed in the management of overdosage with any drugs effective in the treatment of major depressive disorder.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, or exchange transfusion are unlikely to be of benefit.

A specific caution involves patients who are taking or have recently taken paroxetine who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see PRECAUTIONS: *Drugs Metabolized by Cytochrome CYP2D6*).

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. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION

Major Depressive Disorder: *Usual Initial Dosage:* Paroxetine tablets should be administered as a single daily dose with or without food, usually in the morning. The recommended initial dose is 20 mg/day. Patients were dosed in a range of 20 to 50 mg/day in the clinical trials demonstrating the effectiveness of paroxetine tablets in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, the full effect may be delayed. Some patients not responding to a 20 mg dose may benefit from dose increases, in 10 mg/day increments, up to a maximum of 50 mg/day. Dose changes should occur at intervals of at least 1 week.

Maintenance Therapy: There is no body of evidence available to answer the question of how long the patient treated with paroxetine tablets should remain on it. It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Whether the dose needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Systematic evaluation of the efficacy of paroxetine tablets have shown that efficacy is maintained for periods of up to 1 year with doses that averaged about 30 mg.

Obsessive Compulsive Disorder: *Usual Initial Dosage:* Paroxetine tablets should be administered as a single daily dose with or without food, usually in the morning. The recommended dose of paroxetine tablets in the treatment of OCD is 40 mg daily. Patients should be started on 20 mg/day and the dose can be increased in 10 mg/day increments. Dose changes should occur at intervals of at least 1 week. Patients were dosed in a range of 20 to 60 mg/day in the clinical trials demonstrating the effectiveness of paroxetine tablets in the treatment of OCD. The maximum dosage should not exceed 60 mg/day.

Maintenance Therapy: Long-term maintenance of efficacy was demonstrated in a 6-month relapse prevention trial. In this trial, patients with OCD assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY: Clinical Trials). OCD is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Panic Disorder: *Usual Initial Dosage:* Paroxetine tablets should be administered as a single daily dose with or without food, usually in the morning. The target dose of paroxetine tablets in the treatment of panic disorder is 40 mg/day. Patients should be started on 10 mg/day. Dose changes should occur in 10 mg/day increments and at intervals of at least 1 week. Patients were dosed in a range of 10 to 60 mg/day in the clinical trials demonstrating the effectiveness of paroxetine tablets. The maximum dosage should not exceed 60 mg/day.

Maintenance Therapy: Long-term maintenance of efficacy was demonstrated in a 3-month relapse prevention trial. In this trial, patients with panic disorder assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY: Clinical Trials). Panic disorder is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Social Anxiety Disorder: *Usual Initial Dosage:* Paroxetine tablets should be administered as a single daily dose with or without food, usually in the morning. The recommended and initial dosage is 20 mg/day. In clinical trials the effectiveness of paroxetine tablets were demonstrated in patients dosed in a range of 20 to 60 mg/day. While the safety of paroxetine tablets have been evaluated in patients with social anxiety disorder at doses up to 60 mg/day, available information does not suggest any additional benefit for doses above 20 mg/day (see CLINICAL PHARMACOLOGY: Clinical Trials).

Maintenance Therapy: There is no body of evidence available to answer the question of how long the patient treated with paroxetine tablets should remain on it. Although the efficacy of paroxetine tablets beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials, social anxiety disorder is recognized as a chronic condition, and it is reasonable to consider continuation of treatment for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Generalized Anxiety Disorder: *Usual Initial Dosage:* Paroxetine tablets should be administered as a single daily dose with or without food, usually in the morning. In clinical trials the effectiveness of paroxetine tablets were demonstrated in patients dosed in a range of 20 to 50 mg/day. The recommended starting dosage and the established effective dosage is 20 mg/day. There is not sufficient evidence to suggest a greater benefit to doses higher than 20 mg/day. Dose changes should occur in 10 mg/day increments and at intervals of at least 1 week.

Maintenance Therapy: Systematic evaluation of continuing paroxetine tablets for periods of up to 24 weeks in patients with Generalized Anxiety Disorder who had responded while taking paroxetine tablets during an 8-week acute treatment phase has demonstrated a benefit of such maintenance (see CLINICAL PHARMACOLOGY: Clinical Trials). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

Special Populations: *Treatment of Pregnant Women During the Third Trimester:* Neonates exposed to paroxetine tablets and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see WARNINGS: Usage in Pregnancy). When treating pregnant women with paroxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.

Dosage for Elderly or Debilitated Patients, and Patients With Severe Renal or Hepatic Impairment: The recommended initial dose is 10 mg/day for elderly patients, debilitated patients, and/or patients with severe renal or hepatic impairment. Increases may be made if indicated. Dosage should not exceed 40 mg/day.

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 paroxetine tablets. Conversely, at least 14 days should be allowed after stopping paroxetine tablets before starting an MAOI intended to treat psychiatric disorders (see CONTRAINDICATIONS).

Use of Paroxetine Tablets With Other MAOIs, Such as Linezolid or Methylene Blue: Do not start paroxetine tablets in a patient who is being treated with linezolid or intravenous methylene blue because there is 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).

In some cases, a patient already receiving therapy with paroxetine tablets 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, paroxetine tablets 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 paroxetine tablets may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue (see WARNINGS).

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 paroxetine tablets is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use (see WARNINGS).

Discontinuation of Treatment With Paroxetine Tablets: Symptoms associated with discontinuation of paroxetine tablets have been reported (see PRECAUTIONS: *Discontinuation of Treatment with Paroxetine*). Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which paroxetine tablets are being prescribed. 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.

HOW SUPPLIED

Paroxetin tablets, USP 10 mg are white, modified capsule shaped, film coated tablets, debossed with 'C' on the scored side and debossed with '457' on the other side.

Bottle of 30's (Child Resistant)	NDC 59746-457-30
Bottle of 90's (Child Resistant)	NDC 59746-457-90
Bottle of 100's (Child Resistant)	NDC 59746-457-01
Bottle of 100's (Ribbed Stock)	NDC 59746-457-07
Bottle of 1000's (Ribbed Stock)	NDC 59746-457-10

Paroxetin tablets, USP 20 mg are white, modified capsule shaped, film coated tablets, debossed with 'C' on the scored side and debossed with '458' on the other side.

Bottle of 30's (Child Resistant)	NDC 59746-458-30
Bottle of 90's (Child Resistant)	NDC 59746-458-90
Bottle of 100's (Child Resistant)	NDC 59746-458-01
Bottle of 100's (Ribbed Stock)	NDC 59746-458-07
Bottle of 1000's (Ribbed Stock)	NDC 59746-458-10

Paroxetin tablets, USP 30 mg are blue colored, modified capsule shaped, film coated tablets, debossed with 'C' on one side and '459' on the other side.

Bottle of 30's (Child Resistant)	NDC 59746-459-30
Bottle of 90's (Child Resistant)	NDC 59746-459-90
Bottle of 100's (Child Resistant)	NDC 59746-459-01
Bottle of 100's (Ribbed Stock)	NDC 59746-459-07
Bottle of 1000's (Ribbed Stock)	NDC 59746-459-10

Paroxetin tablets, USP 40 mg are white modified capsule shaped, film coated tablets, debossed with 'C' on one side and '460' on the other side.

Bottle of 30's (Child Resistant)	NDC 59746-460-30
Bottle of 90's (Child Resistant)	NDC 59746-460-90
Bottle of 100's (Child Resistant)	NDC 59746-460-01
Bottle of 100's (Ribbed Stock)	NDC 59746-460-07
Bottle of 1000's (Ribbed Stock)	NDC 59746-460-10

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

Manufactured by:
Jubilant Generics Limited
Roorkee - 247661, India

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

Revised: August/2015

What should I tell my healthcare provider before taking paroxetine tablets? Ask if you are not sure.

Before starting paroxetine tablets, tell your healthcare provider if you:

- **are pregnant, may be pregnant, or plan to become pregnant.** There is a possibility that paroxetine tablets may harm your unborn baby, including an increased risk of birth defects, particularly heart defects. Other risks may include a serious condition in which there is not enough oxygen in the baby's blood. Your baby may also have certain other symptoms shortly after birth. Premature births have also been reported in some women who used paroxetine tablets during pregnancy.
- **are breastfeeding.** Paroxetine passes into your milk. Talk to your healthcare provider about the best way to feed your baby while taking paroxetine tablets.
- are taking certain drugs such as:
  - triptans used to treat migraine headache
  - other antidepressants (SSRIs, SNRIs, tricyclics, or lithium) or antipsychotics
  - drugs that affect serotonin, such as lithium, tramadol, tryptophan, St. John's wort
  - certain drugs used to treat irregular heart beats
  - certain drugs used to treat schizophrenia
  - certain drugs used to treat HIV infection
  - certain drugs that affect the blood, such as warfarin, aspirin, and ibuprofen
  - certain drugs used to treat epilepsy
    - atomoxetine
    - cimetidine
    - fentanyl
    - metoprolol
    - pimozide
    - procyclidine
    - tamoxifen
- 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
- have glaucoma (high pressure in the eye)

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Paroxetine tablets 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 paroxetine tablets with your other medicines. Do not start or stop any medicine while taking paroxetine tablets without talking to your healthcare provider first.

If you take paroxetine tablets, you should not take any other medicines that contain paroxetine, including PAXIL CR* and PEXEVA®* (paroxetine mesylate).

How should I take paroxetine tablets?

- Take paroxetine tablets exactly as prescribed. Your healthcare provider may need to change the dose of paroxetine tablets until it is the right dose for you.
- Paroxetine tablets may be taken with or without food.
- If you miss a dose of paroxetine tablets, 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 paroxetine tablets at the same time.
- If you take too much paroxetine tablets, call your healthcare provider or poison control center right away, or get emergency treatment.
- Do not stop taking paroxetine tablets suddenly without talking to your doctor (unless you have symptoms of a severe allergic reaction). If you need to stop taking paroxetine tablets, your healthcare provider can tell you how to safely stop taking it.

What should I avoid while taking paroxetine tablets?

Paroxetine tablets 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 paroxetine tablets affects you. Do not drink alcohol while using paroxetine tablets.

What are possible side effects of paroxetine tablets?

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

Common possible side effects in people who take paroxetine tablets include:

- nausea
- sleepiness
- weakness
- dizziness
- feeling anxious or trouble sleeping
- sexual problems
- sweating
- shaking
- not feeling hungry
- dry mouth
- constipation
- infection
- yawning

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 paroxetine tablets. 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 paroxetine tablets?

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

Keep paroxetine tablets and all medicines out of the reach of children.

General information about paroxetine tablets

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

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

For more information about paroxetine tablets call Jubilant Cadista Pharmaceuticals Inc. at 1-800-313-4623.

What are the ingredients in paroxetine tablets?

Active ingredient: paroxetine hydrochloride, USP

Inactive ingredients in tablets: dibasic calcium phosphate dihydrate, pregelatinized starch, sodium starch glycolate type A, magnesium stearate, hypromellose, titanium dioxide, macrogol and FD&C Blue #2 and polysorbate 80.

*Brand names listed are trademarks of their respective owners and are not trademarks of Jubilant Generics Limited.

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

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Reason for Artwork: New	JUBILANT GENERICS	**Dimension: 880 x 500 mm**
Item Code: 7524000687		**Superseded Item Code: NA**
Substrate: 32 GSM Bible paper with folding size- 43 x 43 mm		
Site Packaging Development Sign and Date	**Production Sign and Date**	**QA Sign and Date**