PAROXETINE- paroxetine tablet, film coated
DIRECT RX

PAROXETINE40 mg

DESCRIPTION

Paroxetine tablets, USP contains paroxetine hydrochloride, an SSRI. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-trans-4R-(4'-fluorophenyl)-3S-[(3',4'- methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate and has the molecular formula of C19H20FNO3•HCl•1/2H2O. The molecular weight is 374.8 (329.4 as free base). The structural formula of paroxetine hydrochloride is:

[Image]

Paroxetine hydrochloride, USP is an odorless, white to off-white crystalline powder, having a melting point range of 120°C to 138°C. It is freely soluble in methanol, soluble in ethanol, sparingly soluble in dichloromethane and slightly soluble in water.

Each paroxetine tablet, USP intended for oral administration contains paroxetine hydrochloride hemihydrate equivalent to 10 mg or 20 mg or 30 mg or 40 mg of paroxetine. Each film-coated tablet contains 10 mg, 20 mg, 30 mg, or 40 mg of paroxetine equivalent to 11.1 mg, 22.2 mg, 33.3 mg or 44.4 mg of paroxetine hydrochloride, respectively. In addition, each tablet contains the following inactive ingredients: dibasic calcium phosphate anhydrous, hypromellose 6 cP, lactose anhydrous, magnesium stearate, polyethylene glycol 6000, povidone, sodium starch glycolate, talc, and titanium dioxide.

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, alpha1-, alpha2-, beta-adrenergic-, dopamine (D2)-, 5-HT1-, 5-HT2-, and histamine (H1)-receptors; antagonism of muscarinic, histaminergic, and alpha1-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 paroxetine tablets, 30 mg 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 Cmax or AUC than females.

Absorption and Distribution:

Paroxetine hydrochloride hemihydrate 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 Cmax, Tmax, Cmin, and T½ 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 Cmax and Cmin values were about 6 and 14 times what would be predicted from single-dose studies. Steady-state drug exposure based on AUC0-24 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 Cmax 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 paroxetine tablets, 30 mg tablets daily for 30 days. 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 Cmin 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, Cmax).

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, Cmin concentrations were about 70% to 80% greater than the respective Cmin 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 tablets 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 tablets were 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 tablets were 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 tablets (HDRS total score <8) during an initial 8-week open-treatment phase and were then randomized to continuation on paroxetine tablets or placebo for 1 year demonstrated a significantly lower relapse rate for patients taking paroxetine tablets (15%) compared to those on placebo (39%). Effectiveness was similar for male and female patients.

Obsessive Compulsive Disorder:

The effectiveness of paroxetine tablets 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 Tablets USP, 20 mg (n = 75)	Paroxetine Tablets USP, 40 mg (n = 66)	Paroxetine Tablets USP, 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 tablets 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 tablets 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 tablets were 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 tablets 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 tablets 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 tablets 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 tablets 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 tablets 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 tablets 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 tablets 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 tablets, were randomized to continuation of paroxetine tablets 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 tablets experienced a significantly lower relapse rate over the subsequent 24 weeks compared to those receiving placebo.

INDICATIONS AND USAGE

Paroxetine tablets are indicated in adults for the treatment of:

Major depressive disorder (MDD)
Obsessive compulsive disorder (OCD)
Panic disorder (PD)

Social anxiety disorder (SAD)
Generalized anxiety disorder (GAD)
Posttraumatic stress disorder (PTSD)

CONTRAINDICATIONS

Paroxetine tablets are contraindicated in patients:

Taking, or within 14 days of stopping, MAOIs (including the MAOIs linezolid and intravenous methylene blue) because of an increased risk of serotonin syndrome [see Warnings and Precautions (5.2), Drug Interactions (7)].
Taking thioridazine because of risk of QT prolongation [see Warnings and Precautions (5.3) and Drug Interactions (7)]
Taking pimozide because of risk of QT prolongation [see Warnings and Precautions (5.3), Drug Interactions (7)].
With known hypersensitivity (e.g., anaphylaxis, angioedema, Stevens-Johnson syndrome) to paroxetine or any of the inactive ingredients in paroxetine tablets [see Adverse Reactions (6.1), (6.2)].

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 health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for paroxetine tablets 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 tablets are 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 torsade 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 to 6, 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 Tablets). 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 tablets 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

5.1 Suicidal Thoughts and Behaviors in Adolescents and Young Adults

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with MDD. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1,000 patients treated are provided in Table 2.

Table 2 Risk Differences of the Number of Patients with Suicidal Thoughts and Behaviors in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric and Adult Patients

Age Range	Drug-Placebo Difference in Number of Patients with Suicidal Thoughts and Behaviors per 1,000 Patients Treated
Increases Compared to Placebo	
< 18 years old	14 additional cases
18 years to 24 years old	5 additional cases
Decreases Compared to Placebo	
25 years to 64 years old	1 fewer case
≥ 65 years old	6 fewer cases

Paroxetine is not approved for use in pediatric patients.

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with MDD that antidepressants delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors.

Monitor all antidepressant-treated patients for any indication for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy, and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing paroxetine, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

5.2 Serotonin Syndrome

SSRIs, including paroxetine, can precipitate serotonin syndrome, a potentially life-threatening condition. The risk is increased with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines and St. John's Wort) and with drugs that impair metabolism of serotonin, i.e., MAOIs [see Contraindications (4), Drug Interactions (7)]. Serotonin syndrome can also occur when these drugs are used alone.

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).

The concomitant use of paroxetine with MAOIs is contraindicated. In addition, do not initiate paroxetine in a patient being treated with MAOIs such as linezolid or intravenous methylene blue. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. If it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking paroxetine discontinue paroxetine before initiating treatment with the MAOI [see Contraindications (4), Drug Interactions (7)].

Monitor all patients taking paroxetine for the emergence of serotonin syndrome. Discontinue treatment with paroxetine and any concomitant serotonergic agents immediately if the above symptoms occur, and initiate supportive symptomatic treatment. If concomitant use of paroxetine with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome and monitor for symptoms.

5.3 Drug Interactions Leading to QT Prolongation

The CYP2D6 inhibitory properties of paroxetine can elevate plasma levels of thioridazine and pimozide. Since thioridazine and pimozide given alone produce prolongation of the QTc interval and increase the risk of serious ventricular arrhythmias, the use of paroxetine is contraindicated in combination with thioridazine and pimozide [see Contraindications (4), Drug Interactions (7), Clinical Pharmacology (12.3)].

5.4 Embryofetal and Neonatal Toxicity

Paroxetine can cause fetal harm when administered to a pregnant woman. Epidemiological studies have shown that infants exposed to paroxetine in the first trimester of pregnancy have an increased risk of cardiovascular malformations. Exposure to paroxetine in late pregnancy may lead to an increased risk for persistent pulmonary hypertension of the newborn (PPNH) and/or neonatal complications requiring prolonged hospitalization, respiratory support, and tube feeding.

If paroxetine is used during pregnancy, or if the patient becomes pregnant while taking paroxetine, the patient should be apprised of the potential hazard to the fetus [see Use in Specific Populations (8.1)].

5.5 Increased Risk of Bleeding

Drugs that interfere with serotonin reuptake inhibition, including paroxetine, increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDS), other antiplatelet 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 drugs that interfere with serotonin reuptake have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Inform patients about the increased risk of bleeding associated with the concomitant use of paroxetine and antiplatelet agents or anticoagulants. For patients taking warfarin, carefully monitor the international normalized ratio.

5.6 Activation of Mania or Hypomania

In patients with bipolar disorder, treating a depressive episode with paroxetine or another antidepressant may precipitate a mixed/manic episode. During controlled clinical trials of paroxetine, hypomania or mania occurred in approximately 1% of paroxetine-treated unipolar patients compared to 1.1% of active-control and 0.3% of placebo-treated unipolar patients. Prior to initiating treatment with paroxetine, screen patients for any personal or family history of bipolar disorder, mania, or hypomania.

5.7 Discontinuation Syndrome

Adverse reactions after discontinuation of serotonergic antidepressants, particularly after abrupt discontinuation, include: nausea, sweating, dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia, such as electric shock sensations), tremor, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. A gradual reduction in dosage rather than abrupt cessation is recommended whenever possible [see Dosage and Administration (2.7)].

During clinical trials of GAD and PTSD, gradual decreases in the daily dose by 10 mg/day at weekly intervals followed by 1 week at 20 mg/day was used before treatment was discontinued. The following adverse reactions 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. Adverse reactions have been reported upon discontinuation of treatment with paroxetine in pediatric patients. The safety and effectiveness of paroxetine in pediatric patients have not been established [see BOXED WARNING, Warnings and Precautions (5.1), Use in Specific Populations (8.4)].

5.8 Seizures

Paroxetine tablets have not been systematically evaluated in patients with seizure disorders. Patients with history of seizures were excluded from clinical studies. During clinical studies, seizures occurred in 0.1% of patients treated with paroxetine. Paroxetine should be prescribed with caution in patients with a seizure disorder. Discontinue paroxetine in any patient who develops seizures.

5.9 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. Cases of angle-closure glaucoma associated with use of paroxetine have been reported. Avoid use of antidepressants, including paroxetine in patients with untreated anatomically narrow angles.

5.10 Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs, including paroxetine. Cases with serum sodium lower than 110 mmol/L have been reported. 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. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

In patients with symptomatic hyponatremia, discontinue paroxetine and institute appropriate medical intervention. Elderly patients, patients taking diuretics, and those who are volume-depleted may be at greater risk of developing hyponatremia with SSRIs [see Use in Specific Populations (8.5)].

5.11 Reduction of Efficacy of Tamoxifen

Some studies have shown that the efficacy of tamoxifen, as measured by the risk of breast cancer relapse/mortality, may be reduced with concomitant use of paroxetine as a result of paroxetine's irreversible inhibition of CYP2D6 and lower blood levels of tamoxifen [see Drug Interactions (7)]. One study suggests that the risk may increase with longer duration of co-administration. However, other studies have failed to demonstrate such a risk. 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.

5.12 Bone Fracture

Epidemiological studies on bone fracture risk during 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.

5.13 Sexual Dysfunction

Use of SSRIs, including paroxetine, may cause symptoms of sexual dysfunction [see Adverse Reactions (6.1)]. In male patients, SSRI use may result in ejaculatory delay or failure, decreased libido, and erectile dysfunction. In female patients, SSRI use may result in decreased libido and delayed or absent orgasm. It is important for prescribers to inquire about sexual function prior to initiation of paroxetine and to inquire specifically about changes in sexual function during treatment, because sexual function may not be spontaneously reported. When evaluating changes in sexual function, obtaining a detailed history (including timing of symptom onset) is important because sexual symptoms may have other causes, including the underlying psychiatric disorder. Discuss potential management strategies to support patients in making informed decisions about treatment.

PRECAUTIONS SECTION II

5.1 Suicidal Thoughts and Behaviors in Adolescents and Young Adults

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among

drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with MDD. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1,000 patients treated are provided in Table 2.

Table 2 Risk Differences of the Number of Patients with Suicidal Thoughts and Behaviors in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric and Adult Patients

Age Range	Drug-Placebo Difference in Number of Patients with Suicidal Thoughts and Behaviors per 1,000 Patients Treated
Increases Compared to Placebo	
< 18 years old	14 additional cases
18 years to 24 years old	5 additional cases
Decreases Compared to Placebo	
25 years to 64 years old	1 fewer case
≥ 65 years old	6 fewer cases

Paroxetine is not approved for use in pediatric patients.

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with MDD that antidepressants delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors.

Monitor all antidepressant-treated patients for any indication for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy, and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing paroxetine, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

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SSRIs, including paroxetine, can precipitate serotonin syndrome, a potentially life-threatening condition. The risk is increased with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines and St. John's Wort) and with drugs that impair metabolism of serotonin, i.e., MAOIs [see Contraindications (4), Drug Interactions (7)]. Serotonin syndrome can also occur when these drugs are used alone.

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).

The concomitant use of paroxetine with MAOIs is contraindicated. In addition, do not initiate paroxetine in a patient being treated with MAOIs such as linezolid or intravenous methylene blue. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. If it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking paroxetine discontinue paroxetine before initiating treatment with the MAOI [see Contraindications (4), Drug Interactions (7)].

Monitor all patients taking paroxetine for the emergence of serotonin syndrome. Discontinue treatment with paroxetine and any concomitant serotonergic agents immediately if the above symptoms occur, and initiate supportive symptomatic treatment. If concomitant use of paroxetine with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome and monitor for symptoms.

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If paroxetine is used during pregnancy, or if the patient becomes pregnant while taking paroxetine, the patient should be apprised of the potential hazard to the fetus [see Use in Specific Populations (8.1)].

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In patients with symptomatic hyponatremia, discontinue paroxetine and institute appropriate medical intervention. Elderly patients, patients taking diuretics, and those who are volume-depleted may be at greater risk of developing hyponatremia with SSRIs [see Use in Specific Populations (8.5)].

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Some studies have shown that the efficacy of tamoxifen, as measured by the risk of breast cancer relapse/mortality, may be reduced with concomitant use of paroxetine as a result of paroxetine's irreversible inhibition of CYP2D6 and lower blood levels of tamoxifen [see Drug Interactions (7)]. One study suggests that the risk may increase with longer duration of co-administration. However, other studies have failed to demonstrate such a risk. 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.

5.12 Bone Fracture

Epidemiological studies on bone fracture risk during 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.

5.13 Sexual Dysfunction

Use of SSRIs, including paroxetine, may cause symptoms of sexual dysfunction [see Adverse Reactions (6.1)]. In male patients, SSRI use may result in ejaculatory delay or failure, decreased libido, and erectile dysfunction. In female patients, SSRI use may result in decreased libido and delayed or absent orgasm. It is important for prescribers to inquire about sexual function prior to initiation of paroxetine and to inquire specifically about changes in sexual function during treatment, because sexual function may not be spontaneously reported. When evaluating changes in sexual function, obtaining a detailed history (including timing of symptom onset) is important because sexual symptoms may have other causes, including the underlying psychiatric disorder. Discuss potential management strategies to support patients in making informed decisions about treatment.

ADVERSE REACTIONS

Associated with Discontinuation of Treatment:

Twenty percent (1,199/6,145) of patients treated with paroxetine tablets 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), and 11.7% (79/676) of patients treated with paroxetine tablets 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 tablets compared to placebo) included the following:

Major Depressive Disorder	OCD	Panic Disorder	Social Anxiety Disorder	Generalized Anxiety Disorder
Paroxetine Tablets				
Placebo Paroxetine Tablets				

Placebo Paroxetine
Tablets
Placebo Paroxetine
Tablets
Placebo Paroxetine
Tablets
Placebo

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

*
Incidence corrected for gender.

CNS
Somnolence 2.3% 0.7% — 1.9% 0.3% 3.4% 0.3% 2.0% 0.2%
Insomnia — — 1.7% 0% 1.3% 0.3% 3.1% 0%
Agitation 1.1% 0.5% —
Tremor 1.1% 0.3% — 1.7% 0%
Anxiety — — — 1.1% 0%
Dizziness — — 1.5% 0% 1.9% 0% 1.0% 0.2%
Gastrointestinal
Constipation — 1.1% 0%
Nausea 3.2% 1.1% 1.9% 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%
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* 1.6% 0% 2.1% 0% 4.9% 0.6% 2.5% 0.5%
Sweating 1.0% 0.3% — 1.1% 0% 1.1% 0.2%
Impotence* — 1.5% 0%
Libido Decreased 1.0% 0%

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 tablets 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 tablets 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 tablets 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 tablets 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 tablets 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*
Body System Preferred Term Paroxetine Tablets Placebo
(n = 421) (n = 421)

*
Events reported by at least 1% of patients treated with paroxetine tablets are included, except the following events which had an incidence on placebo ≥ paroxetine tablets: 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.
†
Includes mostly “lump in throat” and “tightness in throat.”
‡

Percentage corrected for gender.
§
Mostly “ejaculatory delay.”
¶
Includes “anorgasmia,” “erectile difficulties,” “delayed ejaculation/orgasm,” and “sexual dysfunction,” and “impotence.”
#
Includes mostly “difficulty with micturition” and “urinary hesitancy.”
Þ
Includes mostly “anorgasmia” and “difficulty reaching climax/orgasm.”

ADVERSE REACTIONS II

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 tablets 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 tablets 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 tablets 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*
Obsessive
Compulsive
Disorder Panic Disorder Social Anxiety Disorder
Paroxetine
Tablets
Placebo Paroxetine
Tablets
Placebo Paroxetine
Tablets
Placebo
Body System Preferred Term (n = 542) (n = 265) (n = 469) (n = 324) (n = 425) (n = 339)

*
Events reported by at least 2% of OCD, panic disorder, and social anxiety disorder in patients treated with paroxetine tablets are included, except the following events which had an incidence on placebo ≥ paroxetine tablets: [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.
†

Percentage corrected for gender.

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†	23%	1%	21%	1%	28%	1%
Dysmenorrhea	—	—	—	—	5%	4%
Female Genital						
Disorder†	3%	0%	9%	1%	9%	1%
Impotence†	8%	1%	5%	0%	5%	1%
Urinary						

Frequency 3% 1% 2% 0% — —
Urination
Impaired 3% 0% — — — —
Urinary Tract
Infection 2% 1% 2% 1% — —

Generalized Anxiety Disorder:

Table 4 enumerates adverse events that occurred at a frequency of 2% or more among GAD patients on paroxetine tablets 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*
Generalized Anxiety Disorder
Body System Preferred Term Paroxetine
Tablets
Placebo
(n = 735) (n = 529)

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

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 tablets 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 tablets 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 tablets 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*
Obsessive
Compulsive
Disorder Panic Disorder Social Anxiety Disorder
Paroxetine
Tablets
Placebo Paroxetine
Tablets
Placebo Paroxetine
Tablets
Placebo
Body System Preferred Term (n = 542) (n = 265) (n = 469) (n = 324) (n = 425) (n = 339)

*

Events reported by at least 2% of OCD, panic disorder, and social anxiety disorder in patients treated with paroxetine tablets are included, except the following events which had an incidence on placebo ≥ paroxetine tablets: [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.
†
Percentage corrected for gender.

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† 23% 1% 21% 1% 28% 1%
Dysmenorrhea — — — — 5% 4%
Female Genital
Disorder† 3% 0% 9% 1% 9% 1%
Impotence† 8% 1% 5% 0% 5% 1%
Urinary
Frequency 3% 1% 2% 0% — —
Urination
Impaired 3% 0% — — — —
Urinary Tract
Infection 2% 1% 2% 1% — —

Generalized Anxiety Disorder:

Table 4 enumerates adverse events that occurred at a frequency of 2% or more among GAD patients on paroxetine tablets 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.

Generalized Anxiety Disorder
Body System Preferred Term Paroxetine
Tablets
Placebo
(n = 735) (n = 529)

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

ADVERSE REACTIONS III

Generalized Anxiety Disorder:

Table 4 enumerates adverse events that occurred at a frequency of 2% or more among GAD patients on paroxetine tablets 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*
Generalized Anxiety Disorder
Body System Preferred Term Paroxetine
Tablets
Placebo
(n = 735) (n = 529)

*

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

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 25% 2%
Ejaculation†
Female Genital 4% 1%
Disorder†
Impotence† 4% 3%

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 tablets 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 tablets, as shown in Table 5:

Table 5 Treatment-Emergent Adverse Experience Incidence in a Dose-Comparison Trial in the Treatment of Major Depressive Disorder*
Body System/Preferred Term Placebo Paroxetine Tablets
n=51 10 mg
n=102 20 mg
n=104 30 mg
n=101 40 mg
n=102

*
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.

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

ADVERSE REACTIONS IV

The following adverse reactions are included in more detail in other sections of the prescribing information:

Hypersensitivity reactions to paroxetine [see Contraindications (4)]
Suicidal Thoughts and Behaviors [see Warnings and Precautions (5.1)]
Serotonin Syndrome [see Warnings and Precautions (5.2)]
Embryofetal and Neonatal Toxicity [see Warnings and Precautions (5.4)]
Increased Risk of Bleeding [see Warnings and Precautions (5.5)]
Activation of Mania/Hypomania [see Warnings and Precautions (5.6)]
Discontinuation Syndrome [see Warnings and Precautions (5.7)]
Seizures [see Warnings and Precautions (5.8)]
Angle-closure Glaucoma [see Warnings and Precautions (5.9)]
Hyponatremia [see Warnings and Precautions (5.10)]
Bone Fracture [see Warnings and Precautions (5.12)]
Sexual Dysfunction [see Warnings and Precautions (5.13)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data for paroxetine are from:

6-week clinical trials in MDD patients who received paroxetine 20 mg to 50 mg once daily
12-week clinical trials in OCD patients who received paroxetine 20 mg to 60 mg once daily
10- to 12-week clinical trials in PD patients who received paroxetine 10 mg to 60 mg once daily
12-week clinical trials in SAD patients who received paroxetine 20 mg to 50 mg once daily
8-week clinical trials in GAD patients who received paroxetine 10 mg to 50 mg once daily
12-week clinical trials in PTSD patients who received paroxetine 20 mg to 50 mg once daily

Adverse Reactions Leading to Discontinuation

Twenty percent (1,199/6,145) of patients treated with paroxetine in clinical trials in MDD and 16.1% (84/522), 11.8% (64/542), 9.4% (44/469), 10.7% (79/735), and 11.7% (79/676) of patients treated with paroxetine in clinical trials in SAD, OCD, PD, GAD, and PTSD, respectively, discontinued treatment due to an adverse reaction. The most common adverse reactions (≥ 1%) associated with discontinuation (i.e., those adverse reactions associated with dropout at a rate approximately twice or greater for paroxetine compared to placebo) are presented in Table 3.

Table 3 Adverse Reactions Reported as Leading to Discontinuation (≥ 1% of Paroxetine-Treated Patients and Greater than Placebo) in MDD, OCD, PD, SAD, GAD, and PTSD Trials

Where numbers are not provided the incidence of the adverse reactions 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.

MDD
OCD
PD
SAD
GAD
PTSD
Paroxetine
Placebo
Paroxetine
Placebo
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
0.2
2.8
0.6
Insomnia
-
-
1.7
0
1.3
0.3
3.1
0
-
-
Agitation
1.1
0.5
-
-
-
Tremor
1.1
0.3
-
1.7
0
1
0.2
Anxiety
-
-

-
1.1
0
-
-
Dizziness
-
-
1.5
0
1.9
0
1
0.2
-
-
Gastrointestinal
Constipation
-
1.1
0
-
-
Nausea
3.2
1.1
1.9
0
3.2
1.2
4
0.3
2
0.2
2.2
0.6
Diarrhea
1
0.3
-
Dry Mouth
1
0.3
-
-
-
Vomiting
1
0.3
-

1
0
-
-
Flatulence
1
0.3
-
-
Other
Asthenia
1.6
0.4
1.9
0.4
2.5
0.6
1.8
0.2
1.6
0.2
Abnormal
Ejaculationa
1.6
0
2.1
0
4.9
0.6
2.5
0.5
-
-
Sweating
1
0.3
-
1.1
0
1.1
0.2
-
-
Impotencea
-
1.5
0
-
-
Libido

Decreased
1
0
-
-

Most Common Adverse Reactions

The most commonly observed adverse reactions associated with the use of paroxetine (incidence of 5% or greater and at least twice that for placebo) were:

MDD: Asthenia, sweating, nausea, decreased appetite, somnolence, dizziness, insomnia, tremor, nervousness, ejaculatory disturbance, and other male genital disorders.

OCD: Nausea, dry mouth, decreased appetite, constipation, dizziness, somnolence, tremor, sweating, impotence, and abnormal ejaculation.

PD: Asthenia, sweating, decreased appetite, libido decreased, tremor, abnormal ejaculation, female genital disorders, and impotence.

SAD: Sweating, nausea, dry mouth, constipation, decreased appetite, somnolence, tremor, libido decreased, yawn, abnormal ejaculation, female genital disorders, and impotence.

GAD: Asthenia, infection, constipation, decreased appetite, dry mouth, nausea, libido decreased, somnolence, tremor, sweating, and abnormal ejaculation.

PTSD: Asthenia, sweating, nausea, dry mouth, diarrhea, decreased appetite, somnolence, libido decreased, abnormal ejaculation, female genital disorders, and impotence.

Adverse Reactions in Patients with MDD

Table 4 presents the adverse reactions that occurred at an incidence of 1% or more and greater than placebo in clinical trials of paroxetine-treated patients with MDD.

Table 4 Adverse Reactions (≥ l% of Paroxetine-Treated Patients and Greater than Placebo) in 6-Week Clinical Trials for MDD

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

b Percentage corrected for gender.

c Mostly "ejaculatory delay."

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

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

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

Body System/
Adverse Reaction
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 Disordera
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 Disturbanceb,c
13
0
Other Male Genital Disordersb,d
10
0
Urinary Frequency
3
1
Urinary Disordere
3
0
Female Genital Disordersb,f
2
0

Adverse Reactions in Patients with OCD, PD, and SAD

Table 5 presents adverse reactions that occurred at a frequency of 2% or more in clinical trials in patients with OCD, PD, and SAD.

Table 5 Adverse Reactions (≥ 2% of Paroxetine-Treated Patients and Greater than Placebo) in 10 to 12-Week Clinical Trials for OCD, PD, and SAD

a. Percentage corrected for gender.

Body
System/Preferred
Term
Obsessive Compulsive
Disorder
Panic Disorder
Social Anxiety
Disorder
Paroxetine
Placebo
Paroxetine
Placebo
Paroxetine
Placebo
(n = 542)
(n = 265)
(n = 469)
(n = 324)
(n = 425)
(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 Ejaculationa
23
1
21
1
28
1
Dysmenorrhea
-
-

-
-
5
4
Female Genital Disordersa
3
0
9
1
9
1
Impotencea
8
1
5
0
5
1
Urinary Frequency
3
1
2
0
-
-
Urination Impaired
3
0
-
-
-
-
Urinary Tract Infection
2
1
2
1
-
-

Adverse Reactions in Patients with GAD and PTSD

Table 6 presents adverse reactions that occurred at a frequency of 2% or more in clinical trials in patients with GAD and PTSD.

Table 6 Adverse Reactions (≥ 2% of Paroxetine-Treated Patients and Greater than Placebo) in 8- to 12-Week Clinical Trials for GAD and PTSDa

a. Percentage corrected for gender.

Body
System/Preferred Term

Generalized Anxiety
Disorder
Posttraumatic Stress
Disorder
Paroxetine
Placebo
Paroxetine
Placebo
(n = 735)
(n = 529)
(n = 676)
(n = 504)
%
%
%
%
Body as a
Whole
Asthenia
14
6
12
4
Headache
17
14
-
-
Infection
6
3
5
4
Abdominal Pain
4
3
Trauma
6
5
Cardiovascular
Vasodilation
3
1
2
1
Dermatologic
Sweating
6
2
5

1
Gastrointestinal
Nausea
20
5
19
8
Dry Mouth
11
5
10
5
Constipation
10
2
5
3
Diarrhea
9
7
11
5
Decreased
Appetite
5
1
6
3
Vomiting
3
2
3
2
Dyspepsia
-
-
5
3
Nervous System
Insomnia
11
8
12
11
Somnolence
15
5
16
5
Dizziness

6
5
6
5
Tremor
5
1
4
1
Nervousness
4
3
-
-
Libido Decreased
9
2
5
2
Abnormal Dreams
3
Respiratory
System
Respiratory
Disorder
7
5
-
-
Sinusitis
4
3
-
-
Yawn
4
-
2
< 1
Special Senses
Abnormal Vision
2
1
3
1
Urogenital
System
Abnormal
Ejaculationa
25

2
13
2
Female Genital
Disordera
4
1
5
1
Impotencea
4
3
9
1

Dose Dependent Adverse Reactions

MDD

A comparison of adverse reaction rates in a fixed-dose study comparing paroxetine 10 mg, 20 mg, 30 mg, and 40 mg once daily with placebo in the treatment of MDD revealed dose dependent adverse reactions, as shown in Table 7.

Table 7 Adverse Reactions (≥ 5% of Paroxetine-Treated Patients and ≥ Twice the Rate of Placebo) (in a Dose-Comparison Trial in the Treatment of MDD)
Body System/Preferred Term
Placebo
Paroxetine Tablets

n=51
10 mg
n=102
20 mg
n=104
30 mg
n=101
40 mg
n=102

%
%
%
%
%
Body As A Whole

Asthenia
0

2.9
10.6
13.9
12.7
Dermatology

Sweating
2
1
6.7
8.9
11.8
Gastrointestinal

Constipation
5.9
4.9
7.7
9.9
12.7
Decreased Appetite
2
2
5.8
4
4.9
Diarrhea
7.8
9.8
19.2
7.9
14.7
Dry Mouth
2
10.8
18.3
15.8
20.6
Nausea
13.7
14.7
26.9

34.7
36.3
Nervous System

Anxiety
0
2
5.8
5.9
5.9
Dizziness
3.9
6.9
6.7
8.9
12.7
Nervousness
0
5.9
5.8
4
2.9
Paresthesia
0
2.9
1
5
5.9
Somnolence
7.8
12.7
18.3
20.8
21.6
Tremor
0
0
7.7
7.9
14.7
Special Senses

Blurred Vision
2
2.9
2.9
2
7.8
Urogenital System

Abnormal Ejaculation
0
5.8
6.5
10.6
13
Impotence
0
1.9
4.3
6.4
1.9
Male Genital Disorders
0
3.8
8.7
6.4
3.7

OCD

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

PD

In a fixed-dose study comparing placebo and paroxetine 10 mg, 20 mg, and 40 mg in the treatment of PD, the following adverse reactions were shown to be dose-dependent: asthenia, dry mouth, anxiety, libido decreased, tremor, and abnormal ejaculation.

SAD

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

GAD

In a fixed-dose study comparing placebo and paroxetine 20 mg and 40 mg in the treatment of GAD, the following adverse reactions were shown to be dose-dependent: asthenia, constipation, and abnormal ejaculation.

PTSD

In a fixed-dose study comparing placebo and paroxetine 20 mg and 40 mg in the treatment of PTSD, the following adverse reactions were shown to be dose-dependent: impotence and abnormal ejaculation.

Male and Female Sexual Dysfunction

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 SSRI treatment. However, 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 healthcare providers may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in labeling may underestimate their actual incidence.

The percentage of patients reporting symptoms of sexual dysfunction in males and females with MDD, OCD, PD, SAD, GAD, and PTSD are displayed in Table 8.

Table 8 Adverse Reactions Related to Sexual Dysfunction in Patients Treated with Paroxetine in Clinical Trials of MDD, OCD, PD, SAD, GAD, and PTSD

	Paroxetine	Placebo
n (males)	1,446	1,042
	%	%
Decreased Libido	6 to15	0 to 5
Ejaculatory Disturbance	13 to 28	0 to 2
Impotence	2 to 9	0 to 3
n (females)	1,822	1,340
	%	%
Decreased Libido	0 to 9	0 to 2
Orgasmic Disturbance	2 to 9	0 to 1

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

Hallucinations

In pooled clinical trials of paroxetine, hallucinations were observed in 0.2% of paroxetine-treated patients compared to 0.1% of patients receiving placebo.

Less Common Adverse Reactions

The following adverse reactions occurred during the clinical studies of paroxetine and are not included elsewhere in the labeling.

Adverse reactions are categorized by body system and listed in order of decreasing frequency according to the following definitions: Frequent adverse reactions are those occurring on 1 or more occasions in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1,000 patients; rare adverse reactions are those occurring in fewer than 1/1,000 patients.

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, abnormal liver function tests, 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, 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.

6.2 Postmarketing Experience

The following reactions have been identified during post approval use of paroxetine. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship

to drug exposure.

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-Barr¡SR syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, syndrome of inappropriate ADH secretion, prolactinemia and galactorrhea; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, oculogyric crisis which has been associated with concomitant use of pimozide; status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, restless legs syndrome (RLS), ventricular fibrillation, ventricular tachycardia (including torsade de pointes), hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), vasculitic syndromes (such as Henoch-Schönlein purpura), and premature births in pregnant women. There has been a case report of severe hypotension when paroxetine was added to chronic metoprolol treatment.

DRUG ABUSE AND DEPENDENCE

Table 9 presents clinically significant drug interactions with paroxetine.

Table 9 Clinically Significant Drug Interactions with Paroxetine
Monoamine Oxidase Inhibitors (MAOIs)
Clinical Impact
The concomitant use of SSRIs, including paroxetine, and MAOIs increases the risk of serotonin syndrome.
Intervention
Paroxetine is contraindicated in patients taking MAOIs, including MAOIs such as linezolid or intravenous methylene blue [see Dosage and Administration (2.5), Contraindications (4), Warnings and Precautions (5.2)] .
Examples
selegiline, tranylcypromine, isocarboxazid, phenelzine, linezolid, methylene blue
Pimozide and Thioridazine
Clinical Impact
Increased plasma concentrations of pimozide and thioridazine, drugs with a narrow therapeutic index, may increase the risk of QTc prolongation and ventricular arrhythmias.
Intervention
Paroxetine is contraindicated in patients taking pimozide or thioridazine [see Contraindications (4)] .
Other Serotonergic Drugs
Clinical Impact
The concomitant use of serotonergic drugs with paroxetine increases the risk of serotonin syndrome.
Intervention
Monitor patients for signs and symptoms of serotonin syndrome, particularly during treatment initiation and dosage increases. If serotonin syndrome occurs, consider discontinuation of paroxetine and/or concomitant serotonergic drugs [see Warnings and Precautions (5.2)] .
Examples
other SSRIs, SNRIs, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol,

tryptophan, buspirone, St. John's Wort
Drugs that Interfere with Hemostasis (antiplatelet agents and anticoagulants)
Clinical Impact
The concurrent use of an antiplatelet agent or anticoagulant with paroxetine may potentiate the risk of bleeding.
Intervention
Inform patients of the increased risk of bleeding associated with the concomitant use of paroxetine and antiplatelet agents and anticoagulants. For patients taking warfarin, carefully monitor the international normalized ratio [see Warnings and Precautions (5.5)] .
Examples
aspirin, clopidogrel, heparin, warfarin
Drugs Highly Bound to Plasma Protein
Clinical Impact
Paroxetine is a CYP2D6 inhibitor [see Clinical Pharmacology (12.3)] . The concomitant use of paroxetine with a CYP2D6 substrate may increase the exposure of the CYP2D6 substrate.
Intervention
Decrease the dosage of a CYP2D6 substrate if needed with concomitant paroxetine use. Conversely, an increase in dosage of a CYP2D6 substrate may be needed if paroxetine is discontinued.
Examples
propafenone, flecainide, atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, venlafaxine, risperidone.
Tamoxifen
Clinical Impact
Concomitant use of tamoxifen with paroxetine may lead to reduced plasma concentrations of the active metabolite (endoxifen) and reduced efficacy of tamoxifen
Intervention
Consider use of an alternative antidepressant with little or no
CYP2D6 inhibition [see Warnings and Precautions (5.11)] .
Fosamprenavir/Ritonavir
Clinical Impact
Co-administration of fosamprenavir/ritonavir with paroxetine significantly decreased plasma levels of paroxetine.
Intervention
Any dose adjustment should be guided by clinical effect (tolerability and efficacy).

OVERDOSAGE

The following have been reported with paroxetine tablet overdosage:

Seizures, which may be delayed, and altered mental status including coma.

Cardiovascular toxicity, which may be delayed, including QRS and QTc interval prolongation. Hypertension most commonly seen, but rarely can see hypotension alone or with co-ingestants including alcohol.

Serotonin syndrome (patients with a multiple drug overdosage with other proserotonergic drugs may have a higher risk).

Gastrointestinal decontamination with activated charcoal should be considered in patients who present early after a paroxetine overdose.

Consider contacting a Poison Center (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations.

DOSAGE AND ADMINISTRATION

2.1 Administration Information

Administer paroxetine tablets as a single daily dose in the morning, with or without food.

2.2 Recommended Dosage for MDD, OCD, PD, and PTSD

The recommended starting dosages and maximum dosages of paroxetine tablets in patients with MDD, OCD, PD, and PTSD are presented in Table 1.

In patients with an inadequate response, increase dosage in increments of 10 mg per day at intervals of at least 1 week, depending on tolerability.

Table 1 Recommended Daily Dosage of Paroxetine Tablets in Patients with MDD, OCD, PD, and PTSD

Indication	Starting Dose	Maximum Dose
MDD	20 mg	50 mg
OCD	20 mg	60 mg
PD	10 mg	60 mg
PTSD	20 mg	50 mg

2.3 Recommended Dosage for SAD and GAD

SAD

The starting and recommended dosage in patients with SAD is 20 mg daily. In clinical trials the effectiveness of paroxetine tablets was demonstrated in patients dosed in a range of 20 mg to 60 mg daily.

While the safety of paroxetine tablets has been evaluated in patients with SAD at doses up to 60 mg daily, available information does not suggest any additional benefit for doses above 20 mg daily [see Clinical Studies (14.4)].

GAD

The starting and recommended dosage in patients with GAD is 20 mg daily. In clinical trials the effectiveness of paroxetine tablets in GAD was demonstrated in patients dosed in a range of 20 mg to 50 mg daily. There is not sufficient evidence to suggest a greater

benefit to doses higher than 20 mg daily [see Clinical Studies (14.5)].

In patients with an inadequate response, increase dosage in increments of 10 mg per day at intervals of at least 1 week, depending on tolerability.

2.4 Screen for Bipolar Disorder Prior to Starting Paroxetine Tablets

Prior to initiating treatment with paroxetine tablets or another antidepressant, screen patients for a personal or family history of bipolar disorder, mania, or hypomania [see Warnings and Precautions (5.6)].

2.5 Recommended Dosage for Elderly Patients, Patients with Severe Renal Impairment, and Patients with Severe Hepatic Impairment

The recommended initial dosage is 10 mg per day for elderly patients, patients with severe renal impairment, and patients with severe hepatic impairment. Dosage should not exceed 40 mg/day.

2.6 Switching Patients to or from a Monoamine Oxidase Inhibitor (MAOI)

At least 14 days must elapse between discontinuation of a monoamine oxidase inhibitor (MAOI and initiation of paroxetine tablets. In addition, at least 14 days must elapse after stopping paroxetine before starting an MAOI antidepressant [see Contraindications (4), Warnings and Precautions (5.2)].

2.7 Discontinuation of Treatment with Paroxetine Tablets

Adverse reactions may occur upon discontinuation of paroxetine tablets [see Warnings and Precautions (5.7)]. Gradually reduce the dosage rather than stopping paroxetine abruptly whenever possible.

Manufactured by:

Cadila Healthcare Ltd.

India

Distributed by:

Zydus Pharmaceuticals (USA) Inc.

Pennington, NJ 08534

Rev.: 10/21

Medication Guide
Paroxetine (pa rox' e teen) Tablets, USP
What is the most important information I should know about paroxetine tablets?
Paroxetine tablets can cause serious side effects, including:
● Increased risk of suicidal thoughts or actions. Paroxetine tablets and other antidepressant medicines may increase suicidal thoughts and actions in some people 24 years of age and younger, especially within the first few months of treatment or when the dose is changed. Paroxetine tablets are not for use in children.
○ Depression or other mental illnesses are the most important causes of suicidal thoughts and actions.

How can I watch for and try to prevent suicidal thoughts and actions?
○ Pay close attention to any changes, especially sudden changes in mood, behavior,

thoughts or feelings or if you develop suicidal thoughts or actions. This is very important when an antidepressant medicine is started or when the does is changed.
○ Call your healthcare provider right away to report new or sudden changes in mood, behavior, thoughts or feelings or if you develop suicidal thoughts or actions.
○ Keep all follow-up visits with your healthcare provider as scheduled. Call your healthcare provider between visits as needed, especially if you have concerns about symptoms.
Call your healthcare provider or get emergency medical help right away if you have any of the following symptoms, 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 and talking more than what is normal for you
○ other unusual changes in behavior or mood
What are paroxetine tablets?
Paroxetine tablets are prescription medicine used in adults to treat:
● A certain type of depression called Major Depressive Disorder (MDD)
● Obsessive Compulsive Disorder (OCD)
● Panic Disorder (PD)
● Social Anxiety Disorder (SAD)
● Generalized Anxiety Disorder (GAD)
● Posttraumatic Stress Disorder (PTSD)
Do not take paroxetine tablets if you:
● take a monoamine oxidase inhibitor (MAOI)
● have stopped taking an MAOI in the last 14 days
● are being treated with the antibiotic linezolid or the intravenous methylene blue
● are taking pimozide
● are taking thioridazine
● 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.
Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI or one of these medicines, including the antibiotic linezolid or intravenous methylene blue.

Do not start taking an MAOI for at least 14 days after you stop treatment with paroxetine tablets.
Before taking paroxetine tablets, tell your healthcare provider about all your medical conditions, including if you:
● have heart problems
● have or had bleeding problems
● have, or have a family history of, bipolar disorder, mania or hypomania
● have or had seizures or convulsions
● have glaucoma (high pressure in the eye)
● have low sodium levels in your blood
● have bone problems
● have kidney or liver problems

● are pregnant or plan to become pregnant. Paroxetine tablets may harm your unborn baby. Talk to your healthcare provider about the risks to your unborn baby if you take paroxetine tablets during pregnancy. Tell your healthcare provider right away if you become pregnant or think you
● are pregnant during treatment with paroxetine tablets.
● are breastfeeding or plan to breastfeed. Paroxetine passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with paroxetine tablets.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Paroxetine tablets and some other medicines may affect each other causing possible serious side effects. Paroxetine tablets may affect the way other medicines work and other medicines may affect the way paroxetine tablets works.
Especially tell your healthcare provider if you take:
medicines used to treat migraine headaches called triptans
● tricyclic antidepressants
● fentanyl
● lithium
● tramadol
● tryptophan
● buspirone
● amphetamines
● St. John's Wort
● medicines that can affect blood clotting such as aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin
● diuretics
● tamoxifen
● medicines used to treat mood, anxiety, psychotic, or thought disorders, including selective serontonin reuptake (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs)
Ask your healthcare provider if you are not sure if you are taking any of these medicines. Your healthcare provider can tell you if it is safe to take paroxetine tablets with your other medicines.
Do not start or stop any other medicines during treatment with paroxetine tablets without talking to your healthcare provider first. Stopping paroxetine tablets suddenly may cause you to have serious side effects . See, "What are the possible side effects of paroxetine tablets?"

Know the medicines you take. Keep a list of them to show to your healthcare provider and pharmacist when you get a new medicine.
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.
● Take paroxetine tablet 1 time each day in the morning.
● Paroxetine tablets may be taken with or without food.
● If you take too much paroxetine tablets, call your poison control center at 1-800-222-1222 or go to the nearest hospital emergency room right away.
What are possible side effects of paroxetine tablets?
Paroxetine tablets can cause serious side effects, including:

● See, "What is the most important information I should know about paroxetine tablets?"
● Serotonin syndrome. A potentially life-threatening problem called serotonin syndrome can happen when you take paroxetine tablets with certain other medicines. See, "Who should not take paroxetine tablets?" Call your healthcare provider or go to the nearest hospital emergency room right away if you have any of the following signs and symptoms of serotonin syndrome:
○ agitation
○ sweating
○ seeing or hearing things that are not real (hallucinations)
○ flushing
○ confusion
○ high body temperature (hyperthermia)
○ coma
○ shaking (tremors), stiff muscles, or muscle twitching
○ fast heart beat
○ loss of coordination
○ changes in blood pressure
○ seizures
○ dizziness
○ nausea, vomiting, diarrhea
● Eye problems (angle-closure glaucoma). Paroxetine tablets may cause a type of eye problem called angle-closure glaucoma in people with certain other eye conditions. You may want to undergo an eye examination to see if you are at risk and receive preventative treatment if you are. Call your healthcare provider if you have eye pain, changes in your vision, or swelling or redness in or around the eye.
● Medicine interactions. Taking paroxetine tablets with certain other medicines including thioridazine and pimozide may increase the risk of developing a serious heart problem called QT prolongation.
● Seizures (convulsions).
● Manic episodes. Manic episodes may happen in people with bipolar disorder who take paroxetine tablets. Symptoms may include:
○ greatly increased energy
○ severe problems sleeping
○ racing thoughts
○ reckless behavior
○ unusually grand ideas
○ excessive happiness or irritability
○ talking more or faster than usual
● Discontinuation syndrome. Suddenly stopping paroxetine tablets may cause you to have serious side effects. Your healthcare provider may want to decrease your dose slowly. Symptoms may include:
○ nausea
○ electric shock feeling (paresthesia)
○ tiredness
○ sweating
○ tremor
○ problems sleeping
○ changes in your mood
○ anxiety

○ hypomania
irritability and agitation
○ confusion
○ ringing in your ears (tinnitus)
○ dizziness
○ headache
○ seizures
● Low sodium levels in your blood (hyponatremia). Low sodium levels in your blood that may be serious and may cause death, can happen during treatment with paroxetine tablets. Elderly people and people who take certain medicines may be at a greater risk for developing low sodium levels in your blood. Signs and symptoms may include:
○ headache
○ difficulty concentrating
○ memory changes
○ confusion
○ weakness and unsteadiness on your feet which can lead to falls
In more severe or more sudden cases, signs and symptoms include:
○ seeing or hearing things that are not real (hallucinations)
○ fainting
○ seizures
○ coma
○ stopping breathing (respiratory arrest)
● Abnormal bleeding. Taking paroxetine tablets with aspirin, NSAIDs, or blood thinners may increase this risk. Tell your healthcare provider about any unusual bleeding or bruising.
● Bone fractures.
● Sexual problems (dysfunction). Taking selective serotonin reuptake inhibitors (SSRIs), including paroxetine, may cause sexual problems.

Symptoms in males may include:
o Delayed ejaculation or inability to have an ejaculation
o Decreased sex drive
o Problems getting or keeping an erection
Symptoms in females may include:
o Decreased sex drive
o Delayed orgasm or inability to have an orgasm
Talk to your healthcare provider if you develop any changes in your sexual function or if you have any questions or concerns about sexual problems during treatment with paroxetine. There may be treatments your healthcare provider can suggest.

The most common side effects of paroxetine tablets include:

○ male and female sexual function problems
○ weakness (asthenia)
○ constipation
○ decreased appetite
○ diarrhea
○ dizziness
○ dry mouth
○ infection

○ problems sleeping
○ nausea
○ nervousness
○ sleepiness
○ sweating
○ shaking (tremor)
○ yawning

These are not all the possible side effects of paroxetine tablets.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store paroxetine tablets?

● Store paroxetine tablets between 68°F to 77°F (20°C to 25°C).

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

General information about the safe and effective use of paroxetine tablets.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not take 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 symptoms that you have. It may harm them. You may ask your healthcare provider or pharmacist for information about paroxetine tablets that is written for healthcare professionals.

What are the ingredients in paroxetine tablets, USP?

Active ingredient: paroxetine hydrochloride, USP

Inactive ingredients: dibasic calcium phosphate anhydrous, hypromellose 6 cP, lactose anhydrous, magnesium stearate, polyethylene glycol 6000, povidone, sodium starch glycolate, talc, and titanium dioxide.

Medication Guide available at www.zydususa.com/medguides or call 1-877-993-8779.

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India

Distributed by:
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Pennington, NJ 08534

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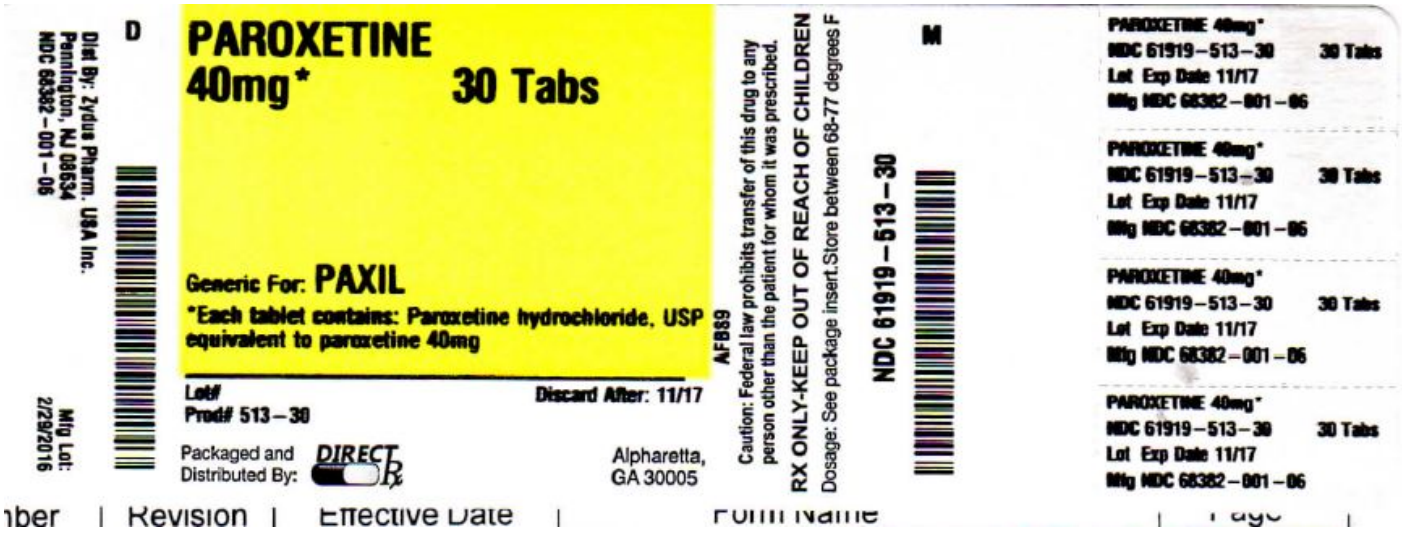
This Medication Guide has been approved by the U.S. Food and Drug Administration.

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL



PAROXETINE

paroxetine tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:61919-513(NDC:68382-001)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
PAROXETINE HYDROCHLORIDE HEMIHYDRATE (UNII: X2ELS050D8) (PAROXETINE - UNII:41VRH5220H)	PAROXETINE	40 mg

Inactive Ingredients	
Ingredient Name	**Strength**
ANHYDROUS DIBASIC CALCIUM PHOSPHATE (UNII: L11K75P92J)	
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
POLYETHYLENE GLYCOL 6000 (UNII: 30IQX730WE)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POVIDONE (UNII: FZ989GH94E)	
TALC (UNII: 7SEV7J4R1U)	

Product Characteristics			
Color	white (TO OFF WHITE)	**Score**	no score
Shape	ROUND	**Size**	11mm
Flavor		**Imprint Code**	ZC18
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:61919-513-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	02/29/2016	11/30/2021
2	NDC:61919-513-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	02/29/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077584	02/29/2016	

Labeler - DIRECT RX (079254320)

Establishment

Name	Address	ID/FEI	Business Operations
DIRECT RX		079254320	repack(61919-513)

Revised: 3/2026 DIRECT RX