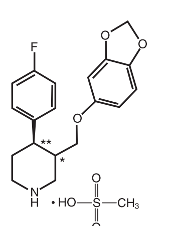
Prescribing Information

PEXEVA™
Brand of
PAROXETINE (as mesylate) tablets

DESCRIPTION

PEXEVA™ (paroxetine mesylate) is an orally administered psychotropic drug with a chemical structure related to paroxetine hydrochloride (Paxil®). It is the mesylate salt of a phenylpiperidine compound identified chemically as (-)-*trans* -4R- (4' - fluorophenyl) - 3S - [(3', 4'-methylenedioxyphenoxy) methyl] piperidine mesylate and has the empirical formula of $C_{19}H_{20}FNO_3 \cdot CH_3SO_3H$. The molecular weight is 425.5 (329.4 as free base). The structural formula is:



paroxetine mesylate

Paroxetine mesylate is an odorless, off-white powder, having a melting point range of 147° to 150°C and a solubility of more than 1 g/mL in water.

Tablets
Each oval, film coated tablet contains paroxetine mesylate equivalent to paroxetine as follows: 10 mg (white); 20 mg (scored, dark orange); 30 mg (yellow); 40 mg (rose). Inactive ingredients consist of dibasic calcium phosphate, hydroxypropyl methylcellulose, hydroxypropylcellulose, magnesium stearate, sodium starch glycolate, titanium dioxide, ferric oxide red (C.I. 77491) (20-mg, and 40-mg only) and ferric oxide yellow (C.I. 77492) (20-mg, 30-mg and 40-mg only).

CLINICAL PHARMACOLOGY

Pharmacodynamics

The efficacy of paroxetine in the treatment of major depressive disorder, obsessive compulsive disorder (OCD), and panic disorder (PD) is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT). Studies at clinically relevant doses in humans have demonstrated that paroxetine blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. *In vitro* radioligand binding studies indicate that paroxetine has little affinity for muscarinic $alpha_1$-, $alpha_2$-, beta-adrenergic-, dopamine (D_2)-, $5\text{-}HT_1$-, $5\text{-}HT_2$- and histamine (H_1)-receptors; antagonism of muscarinic, histaminergic and $alpha_1$-adrenergic receptors has been associated with various anticholinergic, sedative and cardiovascular effects for other psychotropic drugs.

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

Pharmacokinetics

Paroxetine mesylate is completely absorbed after oral dosing of the mesylate salt. In a study in which normal male subjects (n=25) received paroxetine 30 mg tablets daily for 24 days, steady-state paroxetine concentrations were achieved by approximately 13 days for most subjects, although it may take substantially longer in an occasional patient. At steady state, mean values of C_{max}, T_{max}, C_{min} and $T_{1/2}$ were 81.3 ng/mL (CV 41%), 8.1 hr. (CV 56%), 43.2 ng/mL (CV 52%) and 33.2 hr. (CV 52%), respectively. The steady-state C_{max} and C_{min} values were about 7 and 10 times what would be predicted from single-dose studies. Steady-state drug exposure based on $AUC_{0\text{-}24}$ was about 10 times greater than would have been predicted from single-dose data in these subjects.

The excess accumulation is a consequence of the fact that one of the enzymes that metabolizes paroxetine is readily saturable.

In steady-state dose proportionality studies involving elderly and nonelderly patients, at doses of 20 to 40 mg daily for the elderly and 20 to 50 mg daily for the nonelderly, some nonlinearity was observed in both populations, again reflecting a saturable metabolic pathway. In comparison to C_{min} values after 20 mg daily, values after 40 mg were only about 2 to 3 times greater than doubled.

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

Paroxetine 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 cytochrome $P_{450}IID_6$. 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).

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.

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

Protein Binding: 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.

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 was approximately 4 times greater than seen in normal volunteers. Patients with creatinine clearance of 30 to 60 ml/min and patients with hepatic functional impairment had about a 2-fold increase in plasma concentrations (AUC, C_{max}).

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

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

Clinical Trials

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

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

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

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

Outcome Classification (%) on CGI-Global Improvement Item for Completers in Study 1

Outcome Classification	Placebo (N=74)	Paroxetine 20 mg (N=75)	Paroxetine 40 mg (N=66)	Paroxetine 60 mg (N=66)
Worse	14%	7%	7%	3%
No Change	44%	35%	22%	19%
Minimally Improved	24%	33%	29%	34%
Much Improved	11%	18%	22%	24%
Very Much Improved	7%	7%	20%	20%

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

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

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

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

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

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

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

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

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

INDICATIONS AND USAGE

Major Depressive Disorder
PEXEVA™ (paroxetine mesylate) is indicated for the treatment of major depressive disorder.

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

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

The efficacy of paroxetine in maintaining a response in major depressive disorder for up to 1 year was demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY).

Nevertheless, the physician who elects to use PEXEVA™ for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

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

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

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

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

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

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

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

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

CONTRAINDICATIONS

Concomitant use in patients taking either monoamine oxidase inhibitors (MAOIs) or thioridazine is contraindicated (see WARNINGS and PRECAUTIONS).

PEXEVA™ (paroxetine mesylate) tablets are contraindicated in patients with a hypersensitivity to paroxetine or any of the inactive ingredients in PEXEVA™ (paroxetine mesylate) tablets.

WARNINGS

Potential for Interaction with Monoamine Oxidase Inhibitors.

In patients receiving another serotonin reuptake inhibitor drug in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued that drug and have been started on a MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. While there are no human data showing such an interaction with paroxetine, limited animal data on the effects of combined use of paroxetine and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that paroxetine not be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. At least 2 weeks should be allowed after stopping PEXEVA™ before starting a MAOI.

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 $P_{450}IID_6$, 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).

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

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

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Prescriptions for paroxetine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

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).

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

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

PRECAUTIONS

General

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

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

Because of well-established comorbidity between major depressive disorder and other psychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric disorders.

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

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

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

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

Hyponatremia: Several cases of hyponatremia have been reported. The hyponatremia appeared to be reversible when paroxetine was discontinued. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted.

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

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

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

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

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

Information for Patients

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

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

Physicians are advised to discuss the following issues with patients for whom they prescribe PEXEVA™ (paroxetine mesylate):

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

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

Concomitant Medication: Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions. Patients should be made aware that paroxetine, the active ingredient in PEXEVA™, is also the active ingredient of Paxil and that these two medications should not be taken concomitantly.

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

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

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

Laboratory Tests

There are no specific laboratory tests recommended.

Paxil (paroxetine hydrochloride)

Paroxetine, the active ingredient in PEXEVA™, is also the active ingredient of Paxil. Thus, these two agents should not be coadministered.

Drug interactions

Tryptophan: As with other serotonin reuptake inhibitors, an interaction between paroxetine and tryptophan may occur when they are co-administered. Adverse experiences, consisting primarily of headache, nausea, sweating and dizziness, have been reported when tryptophan was administered to patients taking paroxetine. Consequently, concomitant use of paroxetine with tryptophan is not recommended.

Monoamine Oxidase Inhibitors:
See CONTRAINDICATIONS and WARNINGS.

Thioridazine:
See CONTRAINDICATIONS and WARNINGS.

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

Sumatriptan: There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) is clinically warranted, appropriate observation of the patient is advised.

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

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

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

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

Drug Metabolized by Cytochrome $P_{450}IID_6$: Many drugs, including most drugs effective in the treatment of major depressive disorder (paroxetine, other SSRIs and many tricyclics), are metabolized by the cytochrome P_{450} isozyme $P_{450}IID_6$. Like other agents that are metabolized by $P_{450}IID_6$, paroxetine may significantly inhibit the activity of this isozyme. In most patients (>90%), this $P_{450}IID_6$ isozyme is saturated early during paroxetine dosing. In one study, daily dosing of paroxetine (20 mg q.d.) under steady-state conditions increased single dose desipramine (100 mg) C_{max}, AUC and $T_{1/2}$ by an average of approximately two-, five- and three-fold, respectively. Concomitant use of paroxetine with other drugs metabolized by cytochrome $P_{450}IID_6$ has not been formally studied but may require lower doses than usually prescribed for either paroxetine or the other drug.

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

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

At steady state, when the $P_{450}IID_6$ pathway is essentially saturated, paroxetine clearance is governed by alternative P_{450} isozymes, which, unlike $P_{450}IID_6$, show no evidence of saturation. (see PRECAUTIONS-Tricyclic Antidepressants).

Drugs Metabolized by Cytochrome $P_{450}IIIA_4$: An *in vivo* interaction study involving the co-administration under steady-state conditions of paroxetine and terfenadine, a substrate for cytochrome $P_{450}IIIA_4$, revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, *in vitro* studies have shown ketoconazole, a potent inhibitor of $P_{450}IIIA_4$ activity, to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam, and cyclosporine. Based on the assumption that the relationship between paroxetine's *in vitro* K_i and its lack of effect on terfenadine's *in vivo* clearance predicts its effect on other $IIIA_4$ substrates, paroxetine's extent of inhibition of $IIIA_4$ activity is not likely to be of clinical significance.

Tricyclic Antidepressants (TCA): Caution is indicated in the co-administration of tricyclic antidepressants (TCAs) with PEXEVA™, because paroxetine may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is co-administered with PEXEVA™ (see PRECAUTIONS-Drugs Metabolized by Cytochrome $P_{450}IID_6$).

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

Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.): Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentitated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with paroxetine.

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

Lithium: A multiple-dose study has shown that there is no pharmacokinetic interaction between paroxetine and lithium carbonate. However, since there is little clinical experience, the concurrent administration of paroxetine and lithium should be undertaken with caution.

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

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

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

Beta-Blockers: In a study where propranolol (80 mg b.i.d.) was dosed orally for 18 days, the established steady-state plasma concentrations of propranolol were unaltered during co-administration with paroxetine (30 mg q.d.) for the final 10 days. The effects of propranolol on paroxetine have not been evaluated. See ADVERSE REACTIONS-Postmarketing Reports.

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Two-year carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to 2.4 (mouse) and 3.9 (rat) times the maximum recommended human dose (MRHD) for major depressive disorder on a mg/m^2 basis. Because the MRHD for major depressive disorder is slightly less than that for OCD (50 mg vs. 60 mg), the doses used in these carcinogenicity studies were only 2.0 (mouse) and 3.2 (rat) times the MRHD for OCD. There was a significantly greater number of male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50 and 4/50 for control, low-, middle-and high-dose groups, respectively) and a significantly increased linear trend across groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The relevance of these findings to humans is unknown.

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

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

Pregnancy

Teratogenic Effects-Pregnancy Category C
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 equivalent to 9.7 (rat) and 2.2 (rabbit) times the maximum recommended human dose (MRHD) for major depressive disorder (50 mg) and 8.1 (rat) and 1.9 (rabbit) times the MRHD for OCD, on a mg/m^2 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 0.19 times (mg/m^2) the MRHD for major depressive disorder and at 0.16 times (mg/m^2) the MRHD for OCD. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects
Neonates exposed to paroxetine and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs) late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS). When treating a pregnant woman with paroxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION).

Labor and Delivery

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

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in the pediatric population have not been established. (see **WARNINGS - Clinical Worsening and Suicide Risk**).

Geriatric Use

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

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

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

PI-2000-1

PEXEVA™
Brand of
PAROXETINE
(as mesylate) tablets
10 mg, 20 mg, 30 mg, and 40 mg

	Major Depressive Disorder		OCD		Panic Disorder	
	Paroxetine	Placebo	Paroxetine	Placebo	Paroxetine	Placebo
CNS						
Somnolence	2.3%	0.7%	-		1.9%	0.3%
Insomnia	-		1.7%	0%	1.3%	0.3%
Agitation	1.1%	0.5%	-			
Tremor	1.1%	0.3%	-			
Dizziness	-	-	1.5%	0%		
Gastrointestinal						
Constipation	-		1.1%	0%		
Nausea	3.2%	1.1%	1.9%	0%	3.2%	1.2%
Diarrhea	1.0%	0.3%	-			
Dry mouth	1.0%	0.3%	-			
Vomiting	1.0%	0.3%	-			
Other						
Asthenia	1.6%	0.4%	1.9%	0.4%		
Abnormal ejaculation[1]	1.6%	0%	2.1%	0%		
Sweating	1.0%	0.3%	-			
Impotence[1]	-		1.5%	0%		

Where numbers are not provided the incidence of the adverse events in paroxetine patients was not >1% or was not greater than or equal to two times the incidence of placebo.
[1] Incidence corrected for gender.

Commonly Observed Adverse Events

Major Depressive Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine at least twice that for placebo, derived from Table 1 below) were: asthenia, sweating, nausea, decreased appetite, somnolence, dizziness, insomnia, tremor, nervousness, ejaculatory disturbance and other male genital disorders.

Obsessive Compulsive Disorder:

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine at least twice that of placebo, derived from Table 2 below) were: nausea, dry mouth, decreased appetite, constipation, dizziness, somnolence, tremor, sweating, impotence and abnormal ejaculation.

Panic Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine at least twice that for placebo, derived from Table 2 below) were: asthenia, sweating, decreased appetite, libido decreased, tremor, abnormal ejaculation, female genital disorders and impotence.

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 which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the populations studied.

Major Depressive Disorder

Table 1 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 to 50 mg/day. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

TABLE 1

Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder[1]

Body System	Preferred Term	Paroxetine (n=421)	Placebo (n=421)
Body as a Whole	Headache	18%	17%
	Asthenia	15%	6%
Cardiovascular	Palpitation	3%	1%
	Vasodilation	3%	1%
Dermatologic	Sweating	11%	2%
	Rash	2%	1%
Gastrointestinal	Nausea	26%	9%
	Dry Mouth	18%	12%
	Constipation	14%	9%
	Diarrhea	12%	8%
	Decreased Appetite	6%	2%
	Flatulence	4%	2%
	Oropharynx Disorder[2]	2%	0%
	Dyspepsia	2%	1%
Musculoskeletal	Myopathy	2%	1%
	Myalgia	2%	1%
	Myasthenia	1%	0%
Nervous System	Somnolence	23%	9%
	Dizziness	13%	6%
	Insomnia	13%	6%
	Tremor	8%	2%
	Nervousness	5%	3%
	Anxiety	5%	3%
	Paresthesia	4%	2%
	Libido Decreased	3%	0%
	Drugged Feeling	2%	1%
	Confusion	1%	0%
Respiration	Yawn	4%	0%
Special Senses	Blurred Vision	4%	1%
	Taste Perversion	2%	0%
Urogenital System	Ejaculatory Disturbance[3,4]	13%	0%
	Other Male Genital Disorders[3,5]	10%	0%
	Urinary Frequency	3%	1%
	Urination Disorder[6]	3%	0%
	Female Genital Disorders[3,7]	2%	0%

1. Events reported by at least 1% of patients treated with paroxetine are included, except the following events which had an incidence on placebo ≥ paroxetine: abdominal pain, agitation, back pain, chest pain, CNS stimulation, fever, increased appetite, myoclonus, pharyngitis, postural hypotension, respiratory disorder (includes mostly "cold symptoms" or "URI"), trauma and vomiting.
2. Includes mostly "lump in throat" and "tightness in throat."
3. Percentage corrected for gender.
4. Mostly "ejaculatory delay."
5. Includes "anorgasmia," "erectile difficulties," "delayed ejaculation/orgasm," and "sexual dysfunction," and "impotence."
6. Includes mostly "difficulty with micturition" and "urinary hesitancy."
7. Includes mostly "anorgasmia" and "difficulty reaching climax/orgasm."

Obsessive Compulsive Disorder and Panic Disorder

Table 2 enumerates adverse events that occurred at a frequency of 2% or more among OCD patients on paroxetine who participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20 to 60 mg/day or among patients with panic disorder on paroxetine who participated in placebo-controlled trials of 10- to 12-weeks duration in which patients were dosed in a range of 10 to 60 mg/day.

TABLE 2

Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Obsessive Compulsive Disorder and Panic Disorder[1]

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

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

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

TABLE 3

Treatment-Emergent Adverse Experience Incidence in a Dose-Comparison Trial in the Treatment of Major Depressive Disorder*

	Placebo	Paroxetine			
Body System/ Preferred Term	n=51	10 mg n=102	20 mg n=104	30 mg n=101	40 mg n=102
Body as a Whole					
Asthenia	0.0%	2.9%	10.6%	13.9%	12.7%
Dermatology					
Sweating	2.0%	1.0%	6.7%	8.9%	11.8%
Gastrointestinal					
Constipation	5.9%	4.9%	7.7%	9.9%	12.7%
Decreased Appetite	2.0%	2.0%	5.8%	4.0%	4.9%
Diarrhea	7.8%	9.8%	19.2%	7.9%	14.7%
Dry Mouth	2.0%	10.8%	18.3%	15.8%	20.6%
Nausea	13.7%	14.7%	26.9%	34.7%	36.3%
Nervous System					
Anxiety	0.0%	2.0%	5.8%	5.9%	5.9%
Dizziness	3.9%	6.9%	6/7%	8.9%	12.7%
Nervousness	0.0%	5.9%	5.8%	4.0%	2.9%
Paresthesia	0.0%	2.9%	1.0%	5.0%	5.9%
Somnolence	7.8%	12.7%	18.3%	20.8%	21.6%
Tremor	0.0%	0.0%	7.7%	7.9%	14.7%
Special Senses					
Blurred Vision	2.0%	2.9%	2.9%	2.0%	7.8%
Urogenital System					
Abnormal Ejaculation	0.0%	5.8%	6.5%	10.6%	13.0%
Impotence	0.0%	1.9%	4.3%	6.4%	1.9%
Male Genital Disorders	0.0%	3.8%	8.7%	6.4%	3.7%

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

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

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

In flexible dose studies, no new adverse events were observed in patients receiving paroxetine 60 mg compared to any of the other treatment groups.

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

Male and Female Sexual Dysfunction with SSRIs: Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling, are likely to underestimate their actual incidence.

In placebo-controlled clinical trials involving more than 1,800 patients, the ranges for the reported incidence of sexual side effects in males and females with major depressive disorder, OCD and panic disorder are displayed in Table 4 below.

Table 4. Incidence of Sexual Adverse Events in Controlled Clinical Trials

	Paroxetine	Placebo
n (males)	**925**	**655**
Decreased libido	6% - 14%	0% - 5%
Ejaculatory disturbance	13% - 28%	0% - 1%
Impotence	2% - 8%	0% - 1%
n (females)	**932**	**694**
Decreased libido	1% - 9%	0% - 2%
Orgasmic disturbance	2% - 9%	0% - 1%

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

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

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

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

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

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

Other Events Observed During the Premarketing Evaluation of Paroxetine

During its premarketing assessment in major depressive disorder, multiple doses of paroxetine were administered to 6,145 patients in phase 2 and 3 studies. The conditions and duration of exposure to paroxetine varied greatly and included (in overlapping categories) open and double blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose and titration studies. During premarketing clinical trials in OCD and panic disorder, 542 and 469 patients, respectively, received multiple doses of paroxetine. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 9,089 patients exposed to multiple doses of paroxetine who experienced an event of the type cited on at least one occasion while receiving paroxetine. All reported events are included except those already listed in Tables 1 and 2, those reported in terms so general as to be uninformative and those events where a drug cause was remote.

It is important to emphasize that although the events reported occurred during treatment with paroxetine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in the PRECAUTIONS section.

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

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

Digestive System: *infrequent:* bruxism, colitis, dysphagia, eructation, gastritis, gastroenteritis, gingivitis, glossitis, increased salivation, liver function tests abnormal, rectal hemorrhage, ulcerative stomatitis; *rare:* aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, chololithiasis, 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, generalised spasm, tenosynovitis, tetany.

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

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

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

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

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

Postmarketing Reports

Voluntary reports of adverse events in patients taking paroxetine that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome-like events; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide, tremor and trismus; serotonin syndrome, associated in some cases with concomitant use of serotonergic drugs and with drugs which may have impaired paroxetine metabolism (symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor), status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura).

There has been a case report of an elevated phenytoin level after 4 weeks of paroxetine and phenytoin co-administration. There has been a case report of severe hypotension when paroxetine was added to chronic metoprolol treatment.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: Paroxetine is not a controlled substance.

Physical and Psychologic Dependence: Paroxetine has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for history of drug abuse, and such patients should be observed closely for signs of PEXEVA™ misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE

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

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

Overdosage Management: Treatment should consist of those general measures employed in the management of overdosage with any drugs effective in the treatment of major depressive disorder.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for paroxetine are known.

A specific caution involves patients who are taking or have recently taken paroxetine who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation [see Drugs Metabolized by Cytochrome $P_{450}IID_6$ under PRECAUTIONS].

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION

Major Depressive Disorder

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

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

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

Obsessive Compulsive Disorder

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

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

Panic Disorder

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

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

Special Populations

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

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

Switching Patients to or from a Monoamine Oxidase Inhibitor: At least 14 days should elapse between discontinuation of a MAOI and initiation of paroxetine therapy. Similarly, at least 14 days should be allowed after stopping paroxetine before starting an MAOI.

Discontinuation of Treatment with Paroxetine: Symptoms associated with discontinuation of paroxetine have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which paroxetine is being prescribed. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

HOW SUPPLIED

Tablets:

Film-coated, modified-oval tablets as follows:

10 mg white tablets with the inscription POT 10 on one side.

NDC 63672-2010-1 Bottles of 30

20 mg dark orange tablets with the inscription POT 20 on one side. The tablets are scored on both sides.

NDC 63672-2020-1 Bottles of 30

30 mg yellow tablets with the inscription POT 30 on one side.

NDC 63672-2030-1 Bottles of 30

40 mg rose tablets with the inscription POT 40 on one side.

NDC 63672-2040-1 Bottles of 30

Protect from Humidity.
Store at 25°C (77°F); excursions permitted to 15°-30°C (59° and 86°F)
[see USP Controlled Room Temperature]

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