PAROXETINE (Systemic)

Introduction

Revised: 11/02/1999

VA CLASSIFICATION (Primary/Secondary)¾CN603/CN900

Commonly used brand name(s):Paxil; Paxil CR.

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

Category

Antianxiety agent; antidepressant; antiobsessional agent; antipanic agent.

Indications

Accepted

Depressive disorder, major (treatment)¾Paroxetine is indicated for the treatment of major depressive disorder 1, 87.

Treatment of acute depressive episodes typically requires 6 to 12 months of antidepressant therapy 91.

Patients with recurrent or chronic depression may require long-term treatment 91.

Paroxetine has shown effective maintenance of antidepressant response for up to 52 weeks of treatment in a placebo-controlled trial 1.

Obsessive-compulsive disorder (treatment)¾Paroxetine is indicated for the treatment of obsessions and compulsions in patients with obsessive-compulsive disorder 1, 87.

Paroxetine has shown effective relapse prevention for up to 6 months of treatment in a placebo-controlled trial 1.

Panic disorder (treatment)¾Paroxetine is indicated for the treatment of panic disorder, with or without agoraphobia 1, 87.

Social anxiety disorder (treatment)¾Paroxetine is indicated for the treatment of social anxiety disorder or social phobia 100.

Pharmacology/Pharmacokinetics

Note: A wide range of intersubject variability has been observed in the pharmacokinetic parameters of paroxetine 3, 24, 26, 38, 41, 42.

Physicochemical characteristics:

Chemical group¾Phenylpiperidine 1, 8, 41.

Chemically unrelated to other selective serotonin reuptake inhibitors (SSRIs) 1, 54 , or to tricyclic 54, 87 , tetracyclic 1, 87 , or any other currently available antidepressants 1.

Molecular weight¾Paroxetine hydrochloride: 374.8 1, 87

Paroxetine base: 329.37 88

Solubility¾5.4 mg of paroxetine hydrochloride per mL water 1.

Mechanism of action/Effect:

Paroxetine potently and selectively inhibits neuronal serotonin reuptake 3, 8, 18, 75 through antagonism of the serotonin transporter 74.

Its antidepressant, antiobsessional, and antipanic activities are presumed to be linked to potentiation of serotonergic activity in the central nervous system (CNS) 1, 101.

Paroxetine inhibits the active membrane 3 transport mechanism for reuptake of serotonin 3, 41 , which increases concentration of the neurotransmitter at the synaptic cleft 3, 8 and prolongs its activity at synaptic receptor sites 63.

Inhibition of serotonin reuptake also enhances serotonergic neurotransmission 8, 41, 65 by reducing turnover of the neurotransmitter via a negative feedback mechanism 3.

Paroxetine inhibits serotonin reuptake in vitro63 more selectively 2, 40, 64 and more potently 2, 40, 41, 54 than do fluoxetine 2, 40, 41, 54 , sertraline 2, 40, 41, 54 , fluvoxamine 40, 41, 54 , zimeldine 58 , or clomipramine 58, 64.

Paroxetine very 1 weakly inhibits reuptake of norepinephrine 1, 7, 18, 75 and dopamine 1, 3, 7.

Receptor binding studies have demonstrated that paroxetine does not interact directly 3 with central neurotransmitter receptor sites, including alpha 1- 41, 54, 87 , alpha 2- 41, 54, 87 , or beta- 1, 87, 101 adrenoreceptors, and dopamine D 2 41, 54, 87 , serotonin (5-hydroxytryptamine) 5HT 1 1, 41, 101 or 5HT 2 1, 41, 54 , or histamine H 1 8, 41, 54 receptors. Paroxetine has very weak affinity for the muscarinic-cholinergic receptor 8, 41, 54 , and does not inhibit monoamine oxidase 7.

Other actions/effects:

Paroxetine potently 94 inhibits the P450 2D6 (CYP2D6) isoenzyme of the hepatic cytochrome P450 system 70, 93, 94.

In vitro studies indicate that paroxetine is a very weak inhibitor of CYP3A4 1, 101.

This inhibition of isoenzyme CYP3A4 is not likely to be of clinical significance, and an in vivo study revealed no effect of paroxetine on the pharmacokinetics of terfenadine, a CYP3A4 substrate 1, 101.

Paroxetine inhibits serotonin (5-HT) uptake by platelets as well as neurons 1, 101.

At therapeutic doses, paroxetine does not significantly impair psychomotor function 16, 17, 45, 59, 71, 77, 79 and exerts no significant effects on heart rate 16, 32, 45, 48, 58, 60 , blood pressure 16, 32, 44, 45, 48, 58, 60, 67, 80 , or electrocardiogram (ECG) parameters 16, 32, 44, 45, 48, 67.

Also, paroxetine does not appear to induce epileptiform activity 32, 53 or to lower the seizure threshold 40, 53.

Absorption:

Paroxetine is well absorbed 20, 23, 42 from both the suspension and tablet forms 1, 101 , with bioavailability for both dosage forms ranging from 50 to 100% 7, 42.

Bioavailability increases after multiple dosing 20, 87 due to partial saturation of first-pass metabolism 1, 3, 87, 101.

Absorption is not influenced by the presence of food, milk, or antacids 28, 43.

Paroxetine extended-release tablets are designed to control the rate of medication release over 4 to 5 hours 101.

These tablets have an enteric coating that delays the release of medication until the tablets have left the stomach 101.

Distribution:

Paroxetine is extensively distributed into tissues, with only 1% remaining in the systemic circulation 3, 20, 100, 101.

The volume of distribution (Vol D) is large 20, 42 due to the lipophilic nature of paroxetine 20, 42 ; values ranging from 3 to 28 L per kg of body weight (L/kg) have been reported 20.

Paroxetine is distributed into breast milk in concentrations similar to plasma concentrations 3, 20, 87.

Protein binding:

Very high (95%) 20, 29, 78.

In vitro , protein binding of phenytoin and warfarin are not altered by paroxetine 1.

Biotransformation:

Paroxetine undergoes extensive first-pass metabolism in the liver 20, 23, 26, 29, 100, 101.

At least 85% of a paroxetine dose 3 is oxidized 20, 26, 29 to a catechol intermediate 87 that undergoes subsequent methylation 20 and conjugation 20 to clinically inactive 20, 29 glucuronide 13, 42 and sulfate 13, 42 metabolites.

Metabolism is accomplished in part by cytochrome P450 2D6 (CYP2D6) 1, 100, 101 ; saturation of this enzyme at clinical doses appears to account for the nonlinear kinetics observed with increasing dose and duration of paroxetine treatment 1, 41, 87, 101.

The elderly may be more susceptible to the saturation of hepatic metabolic capacity, leading to conversion to nonlinear kinetics, which results in increased plasma concentrations of paroxetine at lower-than-usual doses 5, 23, 42.

Half-life:

Elimination¾

About 24 hours 43, 65, 71, 77, 79 (range, 3 to 65 hours) 7, 20, 42, 43 in healthy adults. Due to partially saturable kinetics 21 , the elimination half-life may be increased in the elderly 20, 21, 23, 78.

However, there is wide intersubject variability 20, 21, 24, 71, 77, 79.

Half-life is prolonged in patients with severe hepatic 8, 42, 78 or renal 20, 25, 42, 53 function impairment.

Onset of action:

Antidepressant effects¾Within 1 to 4 weeks 1, 45 , with improvement in sleep parameters usually occurring in 1 55 to 2 weeks 56.

Antiobsessional and antipanic effects¾May require several weeks to occur 87.

Time to peak concentration:

Immediate-release: Range, 2 to 8 hours 24, 43, 48.

Extended-release: Range, 6 to 10 hours 101.

Time to steady-state serum concentration

Usually achieved in 7 to 14 days in most patients 20, 23, 24, 58 , although it may take considerably longer in some patients 1.

Concentration

Peak plasma¾Following dosing at 30 mg a day for 30 days in healthy volunteers 3, 41 , peak paroxetine plasma concentrations (C max) ranged from 8.6 to 105 mcg/L 3, 41 (0.02 to 0.28 micromoles per L). Peak plasma concentrations are subject to wide interpatient variability 6, 41 because of first-pass metabolism 8 , and increase in a nonlinear fashion with increasing dose because of saturation of CYP2D6 1, 87, 101.

Steady-state serum¾In nonelderly depressed patients receiving long-term dosing of 20 to 50 mg of paroxetine a day, mean steady-state serum concentrations ranged from 48.7 to 117 mcg/L 10 (0.13 to 0.31 micromoles per L). In 15 normal male subjects, steady-state area under the plasma concentration-time curve (AUC) was about eight times greater than was predicted from single-dose kinetics 1.

Nonlinearity is thought to be the result of increased systemic availability due to reduced first-pass metabolism 41 , rather than a decrease in systemic clearance 41.

There appears to be no correlation between paroxetine plasma concentrations and clinical efficacy 38, 43, 67, 75 or incidence of adverse effects 38, 43, 62, 64, 67.

Mean plasma concentrations in patients with creatinine clearances below 30 mL per minute (mL/min) were fourfold greater than those in healthy volunteers 1, 101.

Mean plasma concentrations in patients with creatinine clearances of 30 to 60 mL/min and in patients with hepatic function impairment were twofold greater 1, 101.

Elimination:

Renal¾

In the 10-day period following administration of 30 mg of a paroxetine solution, approximately 64% of the dose was excreted in the urine 1, 20, 101 , of which 2% or less was the parent compound 1, 3, 20, 42, 101.

Fecal¾

In the 10-day period following administration of 30 mg of a paroxetine solution, about 36% of the dose was excreted in the feces 1, 20, 101 , of which unchanged paroxetine comprised less than 1% 1, 101.

Precautions to Consider

Carcinogenicity

In 2-year carcinogenicity studies, a significantly greater number of male rats in the group receiving 3.9 times the maximum recommended human dose (MRHD) of 50 mg for depression and social anxiety disorder (3.2 times the MRHD of 60 mg for obsessive-compulsive disorder and panic disorder) on a mg per square meter of body surface area (mg/m 2) basis exhibited reticulum cell sarcomas than did rats receiving lower doses 100.

Also, there was a significantly increased linear trend across dose groups for occurrence of lymphoreticular tumors in male rats. Female rats were unaffected 100.

In mice receiving up to 2.4 times the MRHD for depression and social anxiety disorder (2 times the MRHD for obsessive-compulsive disorder and panic disorder) on a mg/m 2 basis, there was a dose-

related increase in the number of tumors in mice, but no drug-related increase in the number of mice with tumors 100.

The relevance of these findings to humans is not known. 1, 100

Mutagenicity

Paroxetine demonstrated no genotoxic effects 1, 14, 101 in a battery of five in vitro and two in vivo assays, including the bacterial mutation assay 1, 101 , mouse lymphoma mutation assay 1, 14, 101 , unscheduled DNA synthesis assay 1, 14, 101 , tests for cytogenetic aberrations in vivo in mouse bone marrow 1 and in vitro in human lymphocytes 1 , and a dominant lethal test in rats 1, 14, 101.

Pregnancy/Reproduction

Fertility¾Rats administered paroxetine at doses 2.9 times the MRHD for depression and social anxiety disorder (2.4 times the MRHD for obsessive-compulsive disorder and panic disorder) on a mg/m 2 basis had reduced pregnancy rates 1.

Irreversible reproductive tract lesions occurred in male rats in toxicity studies of 2 to 52 weeks duration 1.

These lesions comprised atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis at doses 4.9 times the MRHD for depression and social anxiety disorder (4.1 times the MRHD for obsessive-compulsive disorder and panic disorder) on a mg/m 2 basis 1 , and vacuolation of the epididymal tubular epithelium at doses 9.8 times the MRHD for depression and social anxiety disorder (8.2 times the MRHD for obsessive-compulsive disorder and panic disorder) on a mg/m 2 basis 1, 100.

Pregnancy¾A prospective study compared birth outcomes of 267 pregnancies that were exposed to the selective serotonin reuptake inhibitors (SSRIs) sertraline (50 mg/day, range 25 to 250 mg/day), paroxetine (30 mg/day, range 10 to 60 mg/day), or fluvoxamine (50 mg/day, range 25 to 200 mg/day) with those of 267 pregnancies that were exposed to medications or medical treatments known to be nonteratogenic 9.

Paroxetine was taken at some time during 97 of the SSRI-exposed pregnancies 9.

Based on interviews with the mothers 6 to 9 months after the births, no differences in the infants" gestational ages or mean birth weights, or in the rates of major malformations, spontaneous or elective abortions, or stillbirths were found between the two groups [9].

Also, no differences were found between infants exposed to SSRIs during the first trimester only and infants exposed to SSRIs throughout gestation [9].

The behavioral effects of in utero paroxetine exposure were not examined [9].

No teratogenic effects [1, 15] or selective toxicity to the fetus [15] were demonstrated in studies in rats and rabbits receiving 9.7 and 2.2 times, respectively, the MRHD for depression and social anxiety disorder on a mg/m [2] basis [1].

However, increased pup death during the first 4 days of lactation occurred in rats given doses 0.19 times the MRHD for depression and social anxiety disorder on a mg/m 2 basis during the last trimester and continuing throughout lactation [1, 100].

FDA Pregnancy Category C [1, 101].

Labor and delivery¾The effect of paroxetine on labor and delivery is not known [1, 101].

Breast-feeding

Paroxetine is distributed into breast milk [90] in concentrations similar to those found in plasma [20].

Pediatrics

No information is available on the relationship of age to the effects of paroxetine in pediatric patients. Safety and efficacy have not been established [1, 87, 101].

Geriatrics

No geriatrics-specific problems have been documented to date in studies that included geriatric patients [1, 101].

However, paroxetine clearance is reduced in the elderly 1, 87, 101.

Also, elderly patients are more likely to have age-related renal function impairment. Reduced paroxetine dosage is recommended for elderly patients 1, 87, 101.

Pharmacogenetics

Approximately 2 to 10% of the adult population are slow metabolizers of CYP2D6 substrates 97.

These patients have a reduced ability to metabolize paroxetine and may be more likely to experience adverse effects 97, 98.

Paroxetine dosage reductions may be necessary in these patients 98.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Paroxetine is a potent 94 inhibitor of cytochrome P450 2D6 (CYP2D6) 93, 94 , but a very weak inhibitor of CYP3A4 1, 93, 101.

Caution should be exercised when paroxetine is coadministered with medications that are metabolized by CYP2D6, such as tricyclic antidepressants 64, 70, 87 , phenothiazines (e.g., thioridazine) 1, 101 , or type IC antiarrhythmics (e.g., encainide, flecainide, or propafenone) 1, 64, 101 , or medications that inhibit CYP2D6, such as quinidine 1, 101.

Dosage reductions of paroxetine and/or the other medication may be necessary 1, 101.

Interactions with medications metabolized by the CYP3A4 isoenzyme are unlikely 1, 100, 101.

At steady state with paroxetine, the CYP2D6 isoenzyme is saturated, and paroxetine metabolism is governed by other hepatic P450 enzymes, which appear to be nonsaturable 1, 100, 101.

Interactions with hepatic enzyme inducers 20, 87 , hepatic enzyme inhibitors 20, 87 , and other medications that are metabolized by the hepatic P450 enzyme system 1, 20 , other than those listed below, have not been studied and the possibility of a significant interaction should be considered 1.

In vitro studies have shown little chance of paroxetine being displaced by other highly protein-bound agents; also, paroxetine is unlikely to displace other highly protein-bound medications 20.

In vivo , however, the potential exists for displacement of one highly protein-bound medication by another; increased free concentrations of the displaced agent could result, increasing the likelihood of adverse effects 1, 100, 101.

Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Alcohol

(although paroxetine has not been shown to alter alcohol metabolism and does not appear to potentiate cognitive and psychomotor 17, 19, 61 effects of alcohol in normal subjects, concomitant use is not recommended 1, 83, 87, 101)

>> Antidepressants, tricyclic (TCAs)

(paroxetine may inhibit TCA metabolism 93, 94, 96 , leading to increased TCA plasma concentrations 94, 95, 96 , and possibly causing adverse effects 95 ; maximum plasma concentration, area under the plasma concentration-time curve, and elimination half-life of a single 100-mg dose of desipramine were increased twofold, fivefold, and threefold, respectively, in subjects at steady-state receiving 20 mg per day of paroxetine 1, 100, 101 ; plasma concentration of the TCA may need to be monitored 1, 100, 101 , and dosage reduction of either the TCA 94, 95 or paroxetine 87 may be required)

>> Astemizole

(because paroxetine inhibits cytochrome P450 enzymes and may increase plasma concentrations of astemizole, thereby increasing the risk of cardiac arrhythmias, concurrent use is not recommended 99)

Cimetidine

(in one study, steady-state plasma concentrations of paroxetine were increased by approximately 50% during concurrent administration of cimetidine 87 ; although the clinical significance of this interaction has not been definitively established 42, 53 , initial dosage reductions are not thought to be necessary, but subsequent dose titration should be based on clinical effects 29)

Digoxin

(mean digoxin area under the plasma concentration-time curve [AUC] decreased 15% in the presence of paroxetine; since there is little clinical experience with this combination, concurrent administration should be undertaken with caution 1, 100, 101)

>> Moclobemide

(because of the potentially fatal effects of concomitant use of paroxetine and nonselective, irreversible monoamine oxidase [MAO] inhibitors, and the increased risk of development of the serotonin syndrome with concomitant use of paroxetine and the selective, reversible MAO-A inhibitor moclobemide, concurrent use is not recommended 86 ; allowing 3 to 7 days to elapse between discontinuing moclobemide and initiating paroxetine therapy, and allowing 2 weeks to elapse between discontinuing paroxetine and initiating moclobemide therapy is advised 86)

>> Monoamine oxidase (MAO) inhibitors, including furazolidone, procarbazine, and selegiline

(concurrent use of MAO inhibitors with paroxetine may result in potentially fatal 1, 87 reactions, which may include confusion, agitation, restlessness, and gastrointestinal symptoms, or possibly hyperpyretic episodes, severe convulsions, hypertensive crises, or the serotonin syndrome; concurrent use is contraindicated 83, 87 , and at least 14 days should elapse between discontinuation of one medication and initiation of the other 1, 87, 100, 101)

Phenobarbital or

Primidone

(primidone is partially metabolized to phenobarbital, which induces many cytochrome P450 enzymes; administration of either of these agents concomitantly with paroxetine may reduce the systemic availability of paroxetine 1, 87 ; no initial dosage adjustments are recommended, but subsequent titration should be based on clinical effects 1, 87, 100, 101)

Phenytoin

(concomitant administration with paroxetine may decrease the systemic availability of either agent 20, 53, 54 ; no initial dosage adjustments are recommended, but subsequent titration should be based on clinical effects 1, 87, 100, 101)

Procyclidine

(concurrent use may increase the systemic availability of procyclidine 3, 20, 87 ; if anticholinergic effects occur, the dosage of procyclidine should be reduced 1, 100, 101)

>> Serotonergics or other medications or substances with serotonergic activity (see Appendix II)

(increased risk of developing the serotonin syndrome, a rare but potentially fatal hyperserotonergic state; symptoms typically occur shortly [hours to days] after the addition of a serotonergic agent, such as paroxetine, to a regimen that includes serotonin-enhancing drugs or an increase in dosage of a serotonergic agent; symptoms include agitation, diaphoresis, diarrhea, fever, hyperreflexia, incoordination, mental status changes [confusion, hypomania], myoclonus, shivering, or tremor; if recognized early, the syndrome usually resolves quickly upon withdrawal of the offending agents 84)

(concurrent use of tryptophan and paroxetine is not recommended 54, 64, 87)

Theophylline

(elevated theophylline concentrations have been reported during concurrent use 1, 100, 101 ; monitoring of theophylline serum concentrations during concurrent use is recommended 1, 100, 101)

>> Warfarin

(although paroxetine does not alter in vitro protein binding of warfarin 1, 100, 101 , a pharmacodynamic 87 interaction may exist that causes an increased bleeding diathesis 29, 87 despite unaltered prothrombin time 3, 87 ; since there is little clinical experience, caution is advised when these agents are used concomitantly 3, 87)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

With physiology/laboratory test values

Hematocrit or

Hemoglobin or

White blood cell counts

(may be decreased 6, 53)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).

Risk-benefit should be considered when the following medical problems exist

>> Hepatic function impairment, severe

(paroxetine plasma concentrations and elimination half-life are increased 1, 87, 100, 101 ; initial dosage should be reduced 4, 62 , starting at 10 mg once a day 1, 8, 100, 101 , and intervals between dosage increases should be lengthened 1, 100, 101)

Mania, history of

(activation of hypomania or mania has been reported in depressed patients treated with paroxetine 7, 10, 53, 87)

Neurological impairment, including developmental delay 91

(risk of seizures may be increased 91)

>> Renal function impairment, severe

(in patients with creatinine clearance < 30 mL per minute [mL/min] and in patients with creatinine clearance between 30 and 60 mL/min, mean plasma paroxetine concentrations were four and two times, respectively, the plasma concentrations seen in healthy volunteers 1, 100, 101 ; initial dosage should be reduced 3, 7, 20, 62 , starting at 10 mg once a day 1, 8, 100, 101 , and intervals between dosage increases should be lengthened 1, 100, 101)

Sensitivity to paroxetine 100, 101

Seizures, history of

(as with other antidepressants, paroxetine should be introduced with caution 1, 87, 100, 101 ; if seizures develop, paroxetine should be discontinued 1, 87, 100, 101)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):

Careful supervision of patients with suicidal tendencies

(recommended especially during early treatment phase before peak effectiveness of paroxetine is achieved 1, 100, 101 ; prescribing the smallest number of tablets necessary for good patient management is recommended to decrease risk of overdose 1, 87, 100, 101)

Side/Adverse Effects

Note: Side effects are usually mild 45, 51, 52, 55, 59, 65, 68 and transient 45, 59, 65, 68 , with evidence of dose-dependency for some of the most common adverse effects 1, 30, 100, 101.

In addition, there is evidence of adaptation with continuing therapy 37, 44, 52, 62, 76 (over 4 to 6 weeks) 1 to some effects, such as nausea 1, 6, 62 and dizziness 1.

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:

Those indicating need for medical attention

Incidence less frequent

Agitation 34, 48, 68; myalgia, myasthenia, or myopathy 1, 100, 101 muscle pain or weakness); palpitation 79 (fast or irregular heartbeat); skin rash 62, 71, 77

Incidence rare

Abnormal bleeding 1, 100, 101, 89 red or purple patches on skin); extrapyramidal symptoms 7, 81, 82; including akinesia 1 or hypokinesia 1 absence of or decrease in body movements); dyskinesia 1 unusual or incomplete body movements); dystonia 1, 81unusual or sudden body or facial movements); inability to move eyes); and dysarthria 1, 100, 101difficulty in speaking); hyponatremia 49, 72, 73 confusion); drowsiness); dryness of mouth); increased thirst); lack of energy); seizures); mania or hypomania 7, 8, 53, 100, 101 talking, feeling, and acting with excitement and activity you cannot control); serotonin syndrome 1, 7, 8, 62, 100, 101 diarrhea); fever); increased sweating); mood or behavior changes); overactive reflexes); racing heartbeat); restlessness); shivering or shaking)

Note: Reports of abnormal bleeding have included a report of impaired platelet aggregation 1, 89 , which could be caused by paroxetine-induced platelet serotonin depletion 1, 89.

However, a causal relationship between paroxetine and abnormal bleeding has not been established 1.

Hyponatremia has been reported mostly in elderly patients, some of whom were taking diuretics or were otherwise volume-depleted 1, 100, 101.

Activation of mania/hypomania occurred in about 1% of unipolar 1, 7, 53 and in about 2% of a subset of bipolar patients 1, 7, 8, 53 during premarketing testing 1, 100, 101.

The serotonin syndrome is most likely to occur shortly (within hours to days) after a paroxetine dosage increase or the addition of another serotonergic agent to the patient"s regimen. The syndrome may include cardiac arrhythmias, coma, disseminated intravascular coagulation, hypertension or hypotension, renal failure, respiratory failure, seizures, or severe hyperthermia. 22

Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Asthenia 44, 50, 51, 53, 100, 101 (unusual tiredness or weakness); constipation 31, 37, 46, 48, 100, 101; diarrhea 45, 52, 66, 67, 100; dizziness 56, 58, 67, 68, 100, 101; drowsiness 33, 36, 47, 55, 57; dryness of mouth 67, 71, 77, 79; headache 31, 48, 67, 68, 101; increased sweating 12, 34, 35, 55, 67, 100, 101; insomnia 67, 68, 71, 77, 100, 101 (trouble in sleeping); nausea 12, 47, 53, 68, 100, 101; sexual dysfunction, especially ejaculatory disturbances 34, 71, 77, 79, 100, 101 or anorgasmia 74 (decreased sexual ability); tremor 35, 71, 77, 79 (trembling or shaking); urinary frequency or retention 56, 79 (problems in urinating); vomiting 12, 37, 58, 68

Note: Dryness of mouth is probably due to a direct effect on the serotonin system rather than cholinergic blockade 44, 71, 77.

Incidence less frequent

Anxiety or nervousness 31, 57, 65, 77; blurred vision 35, 79, 100, 101; decreased libido 34, 56, 71, 79 (decreased sexual desire); decreased 33, 56, 68, 79, 100, 101 or increased 1 appetite; paresthesia 79 (tingling, burning, or prickling sensations); taste perversion 79 (change in sense of taste); weight loss 1 or gain 1, 12

Note: Paroxetine may cause less weight loss than fluoxetine or sertraline 33 ; also, it may cause less weight gain than imipramine, especially in females 76.

Long-term paroxetine treatment may cause increased appetite and weight gain62.

Those indicating the need for medical attention if they occur after medication is discontinued

Agitation 1, 87 , confusion 81, 82 , or restlessness 4; diarrhea 69; dizziness 81, 82, 87 , vertigo 69 , or lightheadedness 69, 87; headache 87; increased sweating 1, 81, 82; insomnia 69, 81, 82, 87 (trouble in sleeping); migraine-like visual disturbances 69 (vision changes); myalgia 69 (muscle pain); nausea 69, 81, 82 or vomiting 69; rhinorrhea 69 (runny nose); tremor 81, 82 (trembling or shaking); unusual tiredness or weakness 69

Note: Discontinuation symptoms, if they occur, usually start 1 to 4 days after stopping paroxetine 81 ; however, some patients may experience effects immediately 4.

Instances of withdrawal symptoms occurring in patients after paroxetine dosage was tapered over 7 to 10 days have been reported 69.

Although most effects are generally mild and transient 82 , some patients may experience more severe symptoms 69.

Overdose

For specific information on the agents used in the management of paroxetine overdose, see Charcoal, Activated (Oral-Local) monograph.

For more information on the management of overdose or unintentional ingestion, contact a poison control center (see Poison Control Center Listing).

Clinical effects of overdose

The following effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:

Dilated pupils 87 large pupils); dizziness 1, 100, 101; drowsiness 1, 87, 100, 101; dryness of mouth 87; flushing of face 1, 100, 101; irritability 87; nausea 1, 87, 100, 101; sinus tachycardia 87racing heartbeat); tremor 87 trembling or shaking); vomiting 1, 87, 100, 101

Treatment of overdose

There is no specific antidote for paroxetine 87.

Treatment is essentially symptomatic and supportive 3.

To decrease absorption¾Decontaminating gastrointestinal tract 3 by, gastric lavage 87, 101 , followed by administration of 20 to 30 grams 87 of activated charcoal 3, 20, 39 every 4 to 6 hours during the first 24 to 48 hours following ingestion 87.

Monitoring¾Taking an electrocardiogram (ECG) and monitoring cardiac function if there is any sign of abnormality 1, 87, 100, 101.

Monitoring vital signs 1, 87, 101.

Supportive care¾Establishing and monitoring airway 1, 87, 100, 101.

Patients in whom intentional overdose is confirmed or suspected should be referred for psychiatric consultation.

Note: Due to the large volume of distribution of paroxetine 42 , forced diuresis 1, 87, 100, 101 , hemodialysis 1, 42, 87, 100, 101 , hemoperfusion 1, 87, 100, 101 , or exchange transfusions 1, 87, 100, 101 are not likely to be of benefit.

If a tricyclic antidepressant has been coingested, the tricyclic toxicity may be prolonged due to inhibition of metabolism by paroxetine 1, 101.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Paroxetine (Systemic) .

In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):

Before using this medication

>> Conditions affecting use, especially:

Sensitivity to paroxetine

Pregnancy¾No difference in birth outcome was found between 267 SSRI-exposed pregnancies (97 to paroxetine) and 267 pregnancies exposed to known nonteratogenic medications or procedures; behavioral effects were not studied

Breast-feeding¾Distributed into breast milkContraindicated medications¾Monoamine oxidase (MAO) inhibitors

Other medications, especially astemizole, moclobemide, serotonergics or other medications or substances with serotonergic activity, tricyclic antidepressants, and warfarin

Other medical problems, especially severe hepatic or renal function impairment

Proper use of this medication

>> Compliance with therapy; not taking more or less medicine than prescribed

Taking with or without food, on a full or empty stomach, as directed by physician

>> Four or more weeks of therapy may be required before antidepressant effects are achieved; antiobsessional and antipanic effects may require several weeks to achieve

For patients taking oral suspension dosage form¾Shaking well before measuring dose; measuring dose with a calibrated measuring device

For patients taking extended-release tablet dosage form¾Swallowing tablet whole; not chewing or crushing

>> Proper dosing

Taking as soon as possible 87 ; continuing on regular schedule with next dose 87 ; not doubling doses

>> Proper storage

Precautions while using this medication

Regular visits to physician to check progress of therapy

Checking with physician before discontinuing medication; gradual dosage reduction may be recommended 87

>> Not taking paroxetine within 2 weeks of taking a monoamine oxidase (MAO) inhibitor; not starting an MAO inhibitor within 2 weeks of discontinuing paroxetine

Avoiding use of alcoholic beverages

>> Possible blurred vision, drowsiness, impairment of judgment, thinking, or motor skills; caution when driving or doing jobs requiring alertness until effects of medication are known

Side/adverse effects

Possibility of discontinuation symptoms

Signs of potential side effects, especially agitation; myalgia, myasthenia, or myopathy; palpitation; skin rash; abnormal bleeding; extrapyramidal symptoms; hyponatremia; mania or hypomania; serotonin syndrome

General Dosing Information

Paroxetine may be administered once daily 3, 43, 62 , usually in the morning 3, 43, 55, 62 , to diminish sleep disturbances and other adverse effects 3.

Potentially suicidal patients, particularly those who may use alcohol excessively, should not have access to large quantities of this medication 1, 87.

Some clinicians recommend that the patient have immediate access to the smallest total amount of medication necessary for satisfactory patient management 1, 7, 87.

Abrupt discontinuation of paroxetine may result in discontinuation symptoms 81.

It is not known whether tapering the dose will prevent or reduce discontinuation symptoms 87.

Diet/Nutrition

Paroxetine may be taken with or without food 3, 20, 28, 42, 43, 100, 101.

Some clinicians advise their patients to take this medication with food to lessen gastrointestinal side effects 3, 5, 6.

For treatment of adverse effects

Serotonin syndrome¾Serotonergic medications should be discontinued 84.

Treatment is essentially symptomatic and supportive 84.

The nonspecific serotonergic receptor antagonists cyproheptadine and methysergide have been reported to be of some use in shortening the duration of the syndrome 84.

Oral Dosage Forms

PAROXETINE HYDROCHLORIDE ORAL SUSPENSION

Note: The dosing and strength of the available dosage forms are expressed in terms of paroxetine base (not the hydrochloride salt) 1.

Usual adult dose

Antianxiety or

Antidepressant or

Antiobsessional agent ¾

Oral, initially 20 mg (base) once a day, usually in the morning 1, 43, 87.

The dosage may be increased, as needed and tolerated, by 10 mg a day 1, 43, 87 at intervals of at least seven days 1, 87.

Antipanic agent¾

Oral, initially 10 mg (base) once a day, usually in the morning 1, 87.

The dosage may be increased, as needed and tolerated, by 10 mg a day [87, 92] at intervals of at least seven days [1, 87].

Note: For most patients, 20 mg a day is the optimal dosage for treatment of depression [11, 43, 62].

For treatment of obsessive-compulsive disorder and panic disorder, 40 mg a day is the recommended dosage [1, 87].

For all indications, debilitated patients and patients with severe renal or hepatic function impairment should receive an initial dosage of 10 mg (base) a day, with upward titration as needed, up to a maximum of 40 mg a day [1, 8, 64].

Longer intervals should be allowed between dosage increases in patients with renal or hepatic function impairment [1].

Usual adult prescribing limits

Antidepressant¾

50 mg (base) per day [1, 43, 62, 87].

Antianxiety agent or

Antiobsessional agent or

Antipanic agent¾

60 mg (base) per day [1, 87].

Usual pediatric dose

Safety and efficacy have not been established [1, 87].

Usual geriatric dose

Antianxiety or

Antidepressant or

Antiobsessional agent or

Antipanic agent¾

Oral, initially 10 mg (base) once a day 1, 8, 64, 85 , usually in the morning 87.

The dosage may be increased as needed and tolerated 1, 92.

Usual geriatric prescribing limits

Antianxiety or

Antidepressant or

Antiobsessional agent or

Antipanic agent ¾

40 mg (base) a day 1, 3, 62, 64, 87.

Strength(s) usually available

U.S.¾10 mg (base) per 5 mL (Rx)[Paxil (citric acid anhydrate) (FD&C Yellow No. 6) (flavorings) (glycerin) (methylparaben) (microcrystalline cellulose) (polacrilin potassium) (propylparaben) (propylene glycol) (Simethicone Emulsion USP) (sodium citrate dihydrate) (sodium saccharin) (sorbitol)] 1

Canada¾Not commercially available.

Packaging and storage:

Store at or below 25 °C (77 °F) 1 , unless otherwise specified by manufacturer.

Auxiliary labeling:

- Avoid alcoholic beverages.
- May cause drowsiness.
- Shake well before using.

Additional information:

Paroxetine hydrochloride oral suspension is orange flavored 1.

PAROXETINE HYDROCHLORIDE TABLETS

Note: The dosing and strength of the available dosage forms are expressed in terms of paroxetine base (not the hydrochloride salt) 1, 87.

Usual adult dose

See Paroxetine Hydrochloride Oral Suspension

Usual adult prescribing limits

See Paroxetine Hydrochloride Oral Suspension

Usual pediatric dose

See Paroxetine Hydrochloride Oral Suspension

Usual geriatric dose

See Paroxetine Hydrochloride Oral Suspension

Usual geriatric prescribing limits

See Paroxetine Hydrochloride Oral Suspension

Strength(s) usually available

U.S.¾10 mg (base) (Rx)[Paxil (dibasic calcium phosphate dihydrate) (hydroxypropyl methylcellulose) (magnesium stearate) (polyethylene glycols) (polysorbate 80) (sodium starch glycolate) (titanium dioxide) (D&C Red No. 30) (and/or D&C Yellow No. 10) (and/or FD&C Blue No. 2) (and/or FD&C Yellow No. 6)] 1

20 mg (base) (Rx)[Paxil (scored) (dibasic calcium phosphate dihydrate) (hydroxypropyl methylcellulose) (magnesium stearate) (polyethylene glycols) (polysorbate 80) (sodium starch glycolate) (titanium dioxide) (D&C Red No. 30) (and/or D&C Yellow No. 10) (and/or FD&C Blue No. 2) (and/or FD&C Yellow No. 6)] 1

30 mg (base) (Rx)[Paxil (dibasic calcium phosphate dihydrate) (hydroxypropyl methylcellulose) (magnesium stearate) (polyethylene glycols) (polysorbate 80) (sodium starch glycolate) (titanium dioxide) (D&C Red No. 30) (and/or D&C Yellow No. 10) (and/or FD&C Blue No. 2) (and/or FD&C Yellow No. 6)] 1

40 mg (base) (Rx)[Paxil (dibasic calcium phosphate dihydrate) (hydroxypropyl methylcellulose) (magnesium stearate) (polyethylene glycols) (polysorbate 80) (sodium starch glycolate) (titanium dioxide) (D&C Red No. 30) (and/or D&C Yellow No. 10) (and/or FD&C Blue No. 2) (and/or FD&C Yellow No. 6)] 1

Canada¾10 mg (base) (Rx)[Paxil (scored) (dibasic calcium phosphate dihydrate USP) (sodium starch glycolate NF) (hydroxypropyl methylcellulose USP) (magnesium stearate NF) (opadry yellow) (opadry clear) 27]

20 mg (base) (Rx)[Paxil (scored) (dibasic calcium phosphate dihydrate USP) (sodium starch glycolate NF) (hydroxypropyl methylcellulose USP) (magnesium stearate NF) (opadry pink) (opadry clear) 87]

30 mg (base) (Rx)[Paxil (dibasic calcium phosphate dihydrate USP) (sodium starch glycolate NF) (hydroxypropyl methylcellulose USP) (magnesium stearate NF) (opadry blue) (opadry clear) 87]

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F) 1, 87 , unless otherwise specified by manufacturer.

Auxiliary labeling:

· Avoid alcoholic beverages.

· May cause drowsiness.

PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS

Usual adult dose

Antidepressant¾

Oral, initially 25 milligrams (mg) once a day, usually in the morning. The dosage may be increased, as needed and tolerated, by 12.5 mg a day at intervals of at least seven days. 101

Note: Debilitated patients and patients with severe renal or hepatic function impairment should receive an initial dosage of 12.5 mg a day, with upward titration as needed, to a maximum of 50 mg a day 101.

Usual adult prescribing limits

Antidepressant¾

62.5 milligrams a day 101.

Usual pediatric dose

Safety and efficacy have not been established 101.

Usual geriatric dose

See Usual adult dose.

Usual geriatric prescribing limits

Antidepressant¾

50 milligrams a day 101.

Strength(s) usually available

U.S.¾12.5 milligrams (Rx)[Paxil CR (hydroxypropyl methylcellulose) (polyvinylpyrrolidone) (lactose monohydrate) (magnesium stearate) (colloidal silicon dioxide) (glyceryl behenate) (methacrylic acid copolymer type C) (sodium lauryl sulfate) (polysorbate 80) (talc) (triethyl citrate) (yellow ferric oxide and/or red ferric oxide)]

25 milligrams (Rx)[Paxil CR (hydroxypropyl methylcellulose) (polyvinylpyrrolidone) (lactose monohydrate) (magnesium stearate) (colloidal silicon dioxide) (glyceryl behenate) (methacrylic acid copolymer type C) (sodium lauryl sulfate) (polysorbate 80) (talc) (triethyl citrate) (yellow ferric oxide and/or red ferric oxide)]

Packaging and storage:

Store between 20 and 25 °C (68 and 77 °F) 101.

Auxiliary labeling:

- Avoid alcoholic beverages.
- May cause drowsiness.
- Swallow whole. Do not crush or chew the tablets.