

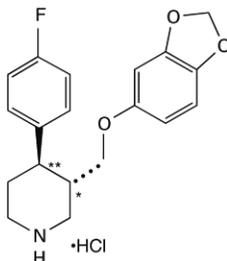
PAXIL CR[®]
(paroxetine hydrochloride)
Controlled-Release Tablets

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of PAXIL CR or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. PAXIL CR is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

DESCRIPTION

PAXIL CR (paroxetine hydrochloride) is an orally administered psychotropic drug with a chemical structure unrelated to other selective serotonin reuptake inhibitors or to tricyclic, tetracyclic, or other available antidepressant or antipanic agents. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-*trans*-4*R*-(4'-fluorophenyl)-3*S*-[(3',4'-methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate and has the empirical formula of C₁₉H₂₀FNO₃•HCl•1/2H₂O. The molecular weight is 374.8 (329.4 as free base). The structural formula of paroxetine hydrochloride is:



Paroxetine hydrochloride is an odorless, off-white powder, having a melting point range of 120° to 138°C and a solubility of 5.4 mg/mL in water.

Each enteric, film-coated, controlled-release tablet contains paroxetine hydrochloride equivalent to paroxetine as follows: 12.5 mg—yellow, 25 mg—pink, 37.5 mg—blue. One layer of

34 the tablet consists of a degradable barrier layer and the other contains the active material in a
35 hydrophilic matrix.

36 Inactive ingredients consist of hypromellose, polyvinylpyrrolidone, lactose monohydrate,
37 magnesium stearate, silicon dioxide, glyceryl behenate, methacrylic acid copolymer type C,
38 sodium lauryl sulfate, polysorbate 80, talc, triethyl citrate, titanium dioxide, polyethylene
39 glycols, and 1 or more of the following colorants: Yellow ferric oxide, red ferric oxide, D&C
40 Red No. 30 aluminum lake, FD&C Yellow No. 6 aluminum lake, D&C Yellow No. 10
41 aluminum lake, FD&C Blue No. 2 aluminum lake.

42 **CLINICAL PHARMACOLOGY**

43 **Pharmacodynamics:** The efficacy of paroxetine in the treatment of major depressive
44 disorder, panic disorder, social anxiety disorder, and premenstrual dysphoric disorder (PMDD) is
45 presumed to be linked to potentiation of serotonergic activity in the central nervous system
46 resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT).
47 Studies at clinically relevant doses in humans have demonstrated that paroxetine blocks the
48 uptake of serotonin into human platelets. In vitro studies in animals also suggest that paroxetine
49 is a potent and highly selective inhibitor of neuronal serotonin reuptake and has only very weak
50 effects on norepinephrine and dopamine neuronal reuptake. In vitro radioligand binding studies
51 indicate that paroxetine has little affinity for muscarinic, α_1 -, α_2 -, beta-adrenergic-,
52 dopamine (D_2)-, 5-HT_{1-} , 5-HT_{2-} , and histamine (H_1)-receptors; antagonism of muscarinic,
53 histaminergic, and α_1 -adrenergic receptors has been associated with various anticholinergic,
54 sedative, and cardiovascular effects for other psychotropic drugs.

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

57 **Pharmacokinetics:** Paroxetine hydrochloride is completely absorbed after oral dosing of a
58 solution of the hydrochloride salt. The elimination half-life is approximately 15 to 20 hours after
59 a single dose of PAXIL CR. Paroxetine is extensively metabolized and the metabolites are
60 considered to be inactive. Nonlinearity in pharmacokinetics is observed with increasing doses.
61 Paroxetine metabolism is mediated in part by CYP2D6, and the metabolites are primarily
62 excreted in the urine and to some extent in the feces. Pharmacokinetic behavior of paroxetine has
63 not been evaluated in subjects who are deficient in CYP2D6 (poor metabolizers).

64 **Absorption and Distribution:** Tablets of PAXIL CR contain a degradable polymeric
65 matrix (GEOMATRIX™) designed to control the dissolution rate of paroxetine over a period of
66 approximately 4 to 5 hours. In addition to controlling the rate of drug release in vivo, an enteric
67 coat delays the start of drug release until tablets of PAXIL CR have left the stomach.

68 Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the
69 hydrochloride salt. In a study in which normal male and female subjects ($n = 23$) received single
70 oral doses of PAXIL CR at 4 dosage strengths (12.5 mg, 25 mg, 37.5 mg, and 50 mg), paroxetine
71 C_{\max} and $AUC_{0-\text{inf}}$ increased disproportionately with dose (as seen also with immediate-release
72 formulations). Mean C_{\max} and $AUC_{0-\text{inf}}$ values at these doses were 2.0, 5.5, 9.0, and 12.5 ng/mL,

73 and 121, 261, 338, and 540 ng•hr./mL, respectively. T_{max} was observed typically between 6 and
74 10 hours post-dose, reflecting a reduction in absorption rate compared with immediate-release
75 formulations. The bioavailability of 25 mg PAXIL CR is not affected by food.

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

78 Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/mL and
79 400 ng/mL, respectively. Under clinical conditions, paroxetine concentrations would normally be
80 less than 400 ng/mL. Paroxetine does not alter the in vitro protein binding of phenytoin or
81 warfarin.

82 **Metabolism and Excretion:** The mean elimination half-life of paroxetine was 15 to
83 20 hours throughout a range of single doses of PAXIL CR (12.5 mg, 25 mg, 37.5 mg, and
84 50 mg). During repeated administration of PAXIL CR (25 mg once daily), steady state was
85 reached within 2 weeks (i.e., comparable to immediate-release formulations). In a repeat-dose
86 study in which normal male and female subjects (n = 23) received PAXIL CR (25 mg daily),
87 mean steady state C_{max} , C_{min} , and AUC_{0-24} values were 30 ng/mL, 20 ng/mL, and 550 ng•hr./mL,
88 respectively.

89 Based on studies using immediate-release formulations, steady-state drug exposure based on
90 AUC_{0-24} was several-fold greater than would have been predicted from single-dose data. The
91 excess accumulation is a consequence of the fact that 1 of the enzymes that metabolizes
92 paroxetine is readily saturable.

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

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

107 Approximately 64% of a 30-mg oral solution dose of paroxetine was excreted in the urine
108 with 2% as the parent compound and 62% as metabolites over a 10-day post-dosing period.
109 About 36% was excreted in the feces (probably via the bile), mostly as metabolites and less than
110 1% as the parent compound over the 10-day post-dosing period.

111 **Other Clinical Pharmacology Information: Specific Populations: Renal and Liver**
112 **Disease:** Increased plasma concentrations of paroxetine occur in subjects with renal and hepatic

113 impairment. The mean plasma concentrations in patients with creatinine clearance below
114 30 mL/min. were approximately 4 times greater than seen in normal volunteers. Patients with
115 creatinine clearance of 30 to 60 mL/min. and patients with hepatic functional impairment had
116 about a 2-fold increase in plasma concentrations (AUC, C_{max}).

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

120 **Elderly Patients:** In a multiple-dose study in the elderly at daily doses of 20, 30, and
121 40 mg of the immediate-release formulation, C_{min} concentrations were about 70% to 80% greater
122 than the respective C_{min} concentrations in nonelderly subjects. Therefore the initial dosage in the
123 elderly should be reduced (see DOSAGE AND ADMINISTRATION).

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

128 **Clinical Trials**

129 **Major Depressive Disorder:** The efficacy of PAXIL CR controlled-release tablets as a
130 treatment for major depressive disorder has been established in two 12-week, flexible-dose,
131 placebo-controlled studies of patients with DSM-IV Major Depressive Disorder. One study
132 included patients in the age range 18 to 65 years, and a second study included elderly patients,
133 ranging in age from 60 to 88. In both studies, PAXIL CR was shown to be significantly more
134 effective than placebo in treating major depressive disorder as measured by the following:
135 Hamilton Depression Rating Scale (HDRS), the Hamilton depressed mood item, and the Clinical
136 Global Impression (CGI)–Severity of Illness score.

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

143 **Panic Disorder:** The effectiveness of PAXIL CR in the treatment of panic disorder was
144 evaluated in three 10-week, multicenter, flexible-dose studies (Studies 1, 2, and 3) comparing
145 paroxetine controlled-release (12.5 to 75 mg daily) to placebo in adult outpatients who had panic
146 disorder (DSM-IV), with or without agoraphobia. These trials were assessed on the basis of their
147 outcomes on 3 variables: (1) the proportions of patients free of full panic attacks at endpoint; (2)
148 change from baseline to endpoint in the median number of full panic attacks; and (3) change
149 from baseline to endpoint in the median Clinical Global Impression Severity score. For Studies 1
150 and 2, PAXIL CR was consistently superior to placebo on 2 of these 3 variables. Study 3 failed
151 to consistently demonstrate a significant difference between PAXIL CR and placebo on any of
152 these variables.

153 For all 3 studies, the mean dose of PAXIL CR for completers at endpoint was approximately
154 50 mg/day. Subgroup analyses did not indicate that there were any differences in treatment
155 outcomes as a function of age or gender.

156 Long-term maintenance effects of the immediate-release formulation of paroxetine in panic
157 disorder were demonstrated in an extension study. Patients who were responders during a
158 10-week double-blind phase with immediate-release paroxetine and during a 3-month
159 double-blind extension phase were randomized to either immediate-release paroxetine or placebo
160 in a 3-month double-blind relapse prevention phase. Patients randomized to paroxetine were
161 significantly less likely to relapse than comparably treated patients who were randomized to
162 placebo.

163 **Social Anxiety Disorder:** The efficacy of PAXIL CR as a treatment for social anxiety
164 disorder has been established, in part, on the basis of extrapolation from the established
165 effectiveness of the immediate-release formulation of paroxetine. In addition, the effectiveness
166 of PAXIL CR in the treatment of social anxiety disorder was demonstrated in a 12-week,
167 multicenter, double-blind, flexible-dose, placebo-controlled study of adult outpatients with a
168 primary diagnosis of social anxiety disorder (DSM-IV). In the study, the effectiveness of
169 PAXIL CR (12.5 to 37.5 mg daily) compared to placebo was evaluated on the basis of (1)
170 change from baseline in the Liebowitz Social Anxiety Scale (LSAS) total score and (2) the
171 proportion of responders who scored 1 or 2 (very much improved or much improved) on the
172 Clinical Global Impression (CGI) Global Improvement score.

173 PAXIL CR demonstrated statistically significant superiority over placebo on both the LSAS
174 total score and the CGI Improvement responder criterion. For patients who completed the trial,
175 64% of patients treated with PAXIL CR compared to 34.7% of patients treated with placebo
176 were CGI Improvement responders.

177 Subgroup analyses did not indicate that there were any differences in treatment outcomes as a
178 function of gender. Subgroup analyses of studies utilizing the immediate-release formulation of
179 paroxetine generally did not indicate differences in treatment outcomes as a function of age, race,
180 or gender.

181 **Premenstrual Dysphoric Disorder:** The effectiveness of PAXIL CR for the treatment of
182 PMDD utilizing a continuous dosing regimen has been established in 2 placebo-controlled trials.
183 Patients in these trials met DSM-IV criteria for PMDD. In a pool of 1,030 patients, treated with
184 daily doses of PAXIL CR 12.5 or 25 mg/day, or placebo the mean duration of the PMDD
185 symptoms was approximately 11 ± 7 years. Patients on systemic hormonal contraceptives were
186 excluded from these trials. Therefore, the efficacy of PAXIL CR in combination with systemic
187 (including oral) hormonal contraceptives for the continuous daily treatment of PMDD is
188 unknown. In both positive studies, patients (N = 672) were treated with 12.5 mg/day or
189 25 mg/day of PAXIL CR or placebo continuously throughout the menstrual cycle for a period of
190 3 menstrual cycles. The VAS-Total score is a patient-rated instrument that mirrors the diagnostic
191 criteria of PMDD as identified in the DSM-IV, and includes assessments for mood, physical
192 symptoms, and other symptoms. 12.5 mg/day and 25 mg/day of PAXIL CR were significantly

193 more effective than placebo as measured by change from baseline to the endpoint on the luteal
194 phase VAS-Total score.

195 In a third study employing intermittent dosing, patients (N = 366) were treated for the 2 weeks
196 prior to the onset of menses (luteal phase dosing, also known as intermittent dosing) with
197 12.5 mg/day or 25 mg/day of PAXIL CR or placebo for a period of 3 months. 12.5 mg/day and
198 25 mg/day of PAXIL CR, as luteal phase dosing, was significantly more effective than placebo
199 as measured by change from baseline luteal phase VAS total score.

200 There is insufficient information to determine the effect of race or age on outcome in
201 these studies.

202 **INDICATIONS AND USAGE**

203 **Major Depressive Disorder:** PAXIL CR is indicated for the treatment of major depressive
204 disorder.

205 The efficacy of PAXIL CR in the treatment of a major depressive episode was established in
206 two 12-week controlled trials of outpatients whose diagnoses corresponded to the DSM-IV
207 category of major depressive disorder (see CLINICAL PHARMACOLOGY: Clinical Trials).

208 A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly
209 every day for at least 2 weeks) depressed mood or loss of interest or pleasure in nearly all
210 activities, representing a change from previous functioning, and includes the presence of at least
211 5 of the following 9 symptoms during the same 2-week period: Depressed mood, markedly
212 diminished interest or pleasure in usual activities, significant change in weight and/or appetite,
213 insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of
214 guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt, or suicidal
215 ideation.

216 The antidepressant action of paroxetine in hospitalized depressed patients has not been
217 adequately studied.

218 PAXIL CR has not been systematically evaluated beyond 12 weeks in controlled clinical
219 trials; however, the effectiveness of immediate-release paroxetine hydrochloride in maintaining a
220 response in major depressive disorder for up to 1 year has been demonstrated in a
221 placebo-controlled trial (see CLINICAL PHARMACOLOGY: Clinical Trials). The physician
222 who elects to use PAXIL CR for extended periods should periodically re-evaluate the long-term
223 usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

224 **Panic Disorder:** PAXIL CR is indicated for the treatment of panic disorder, with or without
225 agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of
226 unexpected panic attacks and associated concern about having additional attacks, worry about
227 the implications or consequences of the attacks, and/or a significant change in behavior related to
228 the attacks.

229 The efficacy of PAXIL CR controlled-release tablets was established in two 10-week trials in
230 panic disorder patients whose diagnoses corresponded to the DSM-IV category of panic disorder
231 (see CLINICAL PHARMACOLOGY: Clinical Trials).

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

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

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

256 The efficacy of PAXIL CR as a treatment for social anxiety disorder has been established, in
257 part, on the basis of extrapolation from the established effectiveness of the immediate-release
258 formulation of paroxetine. In addition, the efficacy of PAXIL CR was established in a 12-week
259 trial, in adult outpatients with social anxiety disorder (DSM-IV). PAXIL CR has not been studied
260 in children or adolescents with social phobia (see CLINICAL PHARMACOLOGY: Clinical
261 Trials).

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

267 **Premenstrual Dysphoric Disorder:** PAXIL CR is indicated for the treatment of PMDD.

268 The efficacy of PAXIL CR in the treatment of PMDD has been established in 3
269 placebo-controlled trials (see CLINICAL PHARMACOLOGY: Clinical Trials).

270 The essential features of PMDD, according to DSM-IV, include markedly depressed mood,
271 anxiety or tension, affective lability, and persistent anger or irritability. Other features include

272 decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite
273 or sleep, and feeling out of control. Physical symptoms associated with PMDD include breast
274 tenderness, headache, joint and muscle pain, bloating, and weight gain. These symptoms occur
275 regularly during the luteal phase and remit within a few days following the onset of menses; the
276 disturbance markedly interferes with work or school or with usual social activities and
277 relationships with others. In making the diagnosis, care should be taken to rule out other cyclical
278 mood disorders that may be exacerbated by treatment with an antidepressant.

279 The effectiveness of PAXIL CR in long-term use, that is, for more than 3 menstrual cycles,
280 has not been systematically evaluated in controlled trials. Therefore, the physician who elects to
281 use PAXIL CR for extended periods should periodically re-evaluate the long-term usefulness of
282 the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

283 **CONTRAINDICATIONS**

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

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

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

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

295 PAXIL CR is contraindicated in patients with a hypersensitivity to paroxetine or to any of the
296 inactive ingredients in PAXIL CR.

297 **WARNINGS**

298 **Clinical Worsening and Suicide Risk:** Patients with major depressive disorder (MDD),
299 both adult and pediatric, may experience worsening of their depression and/or the emergence of
300 suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they
301 are taking antidepressant medications, and this risk may persist until significant remission
302 occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these
303 disorders themselves are the strongest predictors of suicide. There has been a long-standing
304 concern, however, that antidepressants may have a role in inducing worsening of depression and
305 the emergence of suicidality in certain patients during the early phases of treatment. Pooled
306 analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others)
307 showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in
308 children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and
309 other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality
310 with antidepressants compared to placebo in adults beyond age 24; there was a reduction with

311 antidepressants compared to placebo in adults aged 65 and older.

312 The pooled analyses of placebo-controlled trials in children and adolescents with MDD,
313 obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-
314 term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-
315 controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-
316 term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients.
317 There was considerable variation in risk of suicidality among drugs, but a tendency toward an
318 increase in the younger patients for almost all drugs studied. There were differences in absolute
319 risk of suicidality across the different indications, with the highest incidence in MDD. The risk
320 differences (drug vs placebo), however, were relatively stable within age strata and across
321 indications. These risk differences (drug-placebo difference in the number of cases of suicidality
322 per 1,000 patients treated) are provided in Table 1.

323 **Table 1**

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 Patients Treated
Increases Compared to Placebo	
<18	14 additional cases
18-24	5 additional cases
Decreases Compared to Placebo	
25-64	1 fewer case
≥65	6 fewer cases

324
325 No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but
326 the number was not sufficient to reach any conclusion about drug effect on suicide.

327 It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several
328 months. However, there is substantial evidence from placebo-controlled maintenance trials in
329 adults with depression that the use of antidepressants can delay the recurrence of depression.

330 **All patients being treated with antidepressants for any indication should be monitored**
331 **appropriately and observed closely for clinical worsening, suicidality, and unusual changes**
332 **in behavior, especially during the initial few months of a course of drug therapy, or at times**
333 **of dose changes, either increases or decreases.**

334 The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility,
335 aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have
336 been reported in adult and pediatric patients being treated with antidepressants for major
337 depressive disorder as well as for other indications, both psychiatric and nonpsychiatric.
338 Although a causal link between the emergence of such symptoms and either the worsening of
339 depression and/or the emergence of suicidal impulses has not been established, there is concern
340 that such symptoms may represent precursors to emerging suicidality.

341 Consideration should be given to changing the therapeutic regimen, including possibly
342 discontinuing the medication, in patients whose depression is persistently worse, or who are

343 experiencing emergent suicidality or symptoms that might be precursors to worsening depression
344 or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the
345 patient's presenting symptoms.

346 If the decision has been made to discontinue treatment, medication should be tapered, as
347 rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with
348 certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION:
349 *Discontinuation of Treatment With PAXIL CR*, for a description of the risks of discontinuation of
350 PAXIL CR).

351 **Families and caregivers of patients being treated with antidepressants for major**
352 **depressive disorder or other indications, both psychiatric and nonpsychiatric, should be**
353 **alerted about the need to monitor patients for the emergence of agitation, irritability,**
354 **unusual changes in behavior, and the other symptoms described above, as well as the**
355 **emergence of suicidality, and to report such symptoms immediately to healthcare**
356 **providers. Such monitoring should include daily observation by families and caregivers.**

357 Prescriptions for PAXIL CR should be written for the smallest quantity of tablets consistent with
358 good patient management, in order to reduce the risk of overdose.

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

369 **Serotonin Syndrome:** The development of a potentially life-threatening serotonin syndrome
370 has been reported with SNRIs and SSRIs, including PAXIL CR, alone but particularly with
371 concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants,
372 fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort) and with drugs that
373 impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric
374 disorders and also others, such as linezolid and intravenous methylene blue).

375 Serotonin syndrome symptoms may include mental status changes (e.g., agitation,
376 hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood
377 pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor,
378 rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms
379 (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin
380 syndrome.

381 The concomitant use of PAXIL CR with MAOIs intended to treat psychiatric disorders is
382 contraindicated. PAXIL CR should also not be started in a patient who is being treated with

383 MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that
384 provided information on the route of administration involved intravenous administration in the
385 dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by
386 other routes (such as oral tablets or local tissue injection) or at lower doses. There may be
387 circumstances when it is necessary to initiate treatment with an MAOI such as linezolid or
388 intravenous methylene blue in a patient taking PAXIL CR. PAXIL CR should be discontinued
389 before initiating treatment with the MAOI (see CONTRAINDICATIONS and DOSAGE AND
390 ADMINISTRATION).

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

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

397 **Potential Interaction With Thioridazine: Thioridazine administration alone produces**
398 **prolongation of the QTc interval, which is associated with serious ventricular arrhythmias,**
399 **such as torsade de pointes–type arrhythmias, and sudden death. This effect appears to be**
400 **dose related.**

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

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

- 409 • A study based on Swedish national registry data demonstrated that infants exposed to
410 paroxetine during pregnancy (n = 815) had an increased risk of cardiovascular
411 malformations (2% risk in paroxetine-exposed infants) compared to the entire registry
412 population (1% risk), for an odds ratio (OR) of 1.8 (95% confidence interval 1.1 to 2.8). No
413 increase in the risk of overall congenital malformations was seen in the paroxetine-exposed
414 infants. The cardiac malformations in the paroxetine-exposed infants were primarily
415 ventricular septal defects (VSDs) and atrial septal defects (ASDs). Septal defects range in
416 severity from those that resolve spontaneously to those which require surgery.
- 417 • A separate retrospective cohort study from the United States (United Healthcare data)
418 evaluated 5,956 infants of mothers dispensed antidepressants during the first trimester
419 (n = 815 for paroxetine). This study showed a trend towards an increased risk for
420 cardiovascular malformations for paroxetine (risk of 1.5%) compared to other
421 antidepressants (risk of 1%), for an OR of 1.5 (95% confidence interval 0.8 to 2.9). Of the
422 12 paroxetine-exposed infants with cardiovascular malformations, 9 had VSDs. This study

423 also suggested an increased risk of overall major congenital malformations including
424 cardiovascular defects for paroxetine (4% risk) compared to other (2% risk) antidepressants
425 (OR 1.8; 95% confidence interval 1.2 to 2.8).
426 • Two large case-control studies using separate databases, each with >9,000 birth defect
427 cases and >4,000 controls, found that maternal use of paroxetine during the first trimester
428 of pregnancy was associated with a 2- to 3-fold increased risk of right ventricular outflow
429 tract obstructions. In one study the OR was 2.5 (95% confidence interval, 1.0 to 6.0, 7
430 exposed infants) and in the other study the OR was 3.3 (95% confidence interval, 1.3 to
431 8.8, 6 exposed infants).

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

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

451 **Animal Findings:** Reproduction studies were performed at doses up to 50 mg/kg/day in rats
452 and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately
453 8 (rat) and 2 (rabbit) times the maximum recommended human dose (MRHD) on an mg/m²
454 basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was
455 an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last
456 trimester of gestation and continued throughout lactation. This effect occurred at a dose of
457 1 mg/kg/day or approximately one-sixth of the MRHD on an mg/m² basis. The no-effect dose for
458 rat pup mortality was not determined. The cause of these deaths is not known.

459 **Nonteratogenic Effects:** Neonates exposed to PAXIL CR and other SSRIs or serotonin
460 and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed
461 complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such
462 complications can arise immediately upon delivery. Reported clinical findings have included

463 respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty,
464 vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and
465 constant crying. These features are consistent with either a direct toxic effect of SSRIs and
466 SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the
467 clinical picture is consistent with serotonin syndrome (see WARNINGS: Serotonin Syndrome).

468 Infants exposed to SSRIs in pregnancy may have an increased risk for persistent pulmonary
469 hypertension of the newborn (PPHN). PPHN occurs in 1 – 2 per 1,000 live births in the general
470 population and is associated with substantial neonatal morbidity and mortality. Several recent
471 epidemiologic studies suggest a positive statistical association between SSRI use (including
472 PAXIL CR) in pregnancy and PPHN. Other studies do not show a significant statistical
473 association.

474 Physicians should also note the results of a prospective longitudinal study of 201 pregnant
475 women with a history of major depression, who were either on antidepressants or had received
476 antidepressants less than 12 weeks prior to their last menstrual period, and were in remission.
477 Women who discontinued antidepressant medication during pregnancy showed a significant
478 increase in relapse of their major depression compared to those women who remained on
479 antidepressant medication throughout pregnancy.

480 When treating a pregnant woman with PAXIL CR, the physician should carefully consider
481 both the potential risks of taking an SSRI, along with the established benefits of treating
482 depression with an antidepressant. This decision can only be made on a case by case basis (see
483 DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS, Postmarketing Reports).

484 **PRECAUTIONS**

485 **General: Activation of Mania/Hypomania:** During premarketing testing of
486 immediate-release paroxetine hydrochloride, hypomania or mania occurred in approximately
487 1.0% of paroxetine-treated unipolar patients compared to 1.1% of active-control and 0.3% of
488 placebo-treated unipolar patients. In a subset of patients classified as bipolar, the rate of manic
489 episodes was 2.2% for immediate-release paroxetine and 11.6% for the combined active-control
490 groups. Among 1,627 patients with major depressive disorder, panic disorder, social anxiety
491 disorder, or PMDD treated with PAXIL CR in controlled clinical studies, there were no reports
492 of mania or hypomania. As with all drugs effective in the treatment of major depressive disorder,
493 PAXIL CR should be used cautiously in patients with a history of mania.

494 **Seizures:** During premarketing testing of immediate-release paroxetine hydrochloride,
495 seizures occurred in 0.1% of paroxetine-treated patients, a rate similar to that associated with
496 other drugs effective in the treatment of major depressive disorder. Among 1,627 patients who
497 received PAXIL CR in controlled clinical trials in major depressive disorder, panic disorder,
498 social anxiety disorder, or PMDD, 1 patient (0.1%) experienced a seizure. PAXIL CR should be
499 used cautiously in patients with a history of seizures. It should be discontinued in any patient
500 who develops seizures.

501 **Discontinuation of Treatment With PAXIL CR:** Adverse events while discontinuing

502 therapy with PAXIL CR were not systematically evaluated in most clinical trials; however, in
503 recent placebo-controlled clinical trials utilizing daily doses of PAXIL CR up to 37.5 mg/day,
504 spontaneously reported adverse events while discontinuing therapy with PAXIL CR were
505 evaluated. Patients receiving 37.5 mg/day underwent an incremental decrease in the daily dose
506 by 12.5 mg/day to a dose of 25 mg/day for 1 week before treatment was stopped. For patients
507 receiving 25 mg/day or 12.5 mg/day, treatment was stopped without an incremental decrease in
508 dose. With this regimen in those studies, the following adverse events were reported for
509 PAXIL CR, at an incidence of 2% or greater for PAXIL CR and were at least twice that reported
510 for placebo: Dizziness, nausea, nervousness, and additional symptoms described by the
511 investigator as associated with tapering or discontinuing PAXIL CR (e.g., emotional lability,
512 headache, agitation, electric shock sensations, fatigue, and sleep disturbances). These events
513 were reported as serious in 0.3% of patients who discontinued therapy with PAXIL CR.

514 During marketing of PAXIL CR and other SSRIs and SNRIs, there have been spontaneous
515 reports of adverse events occurring upon discontinuation of these drugs, (particularly when
516 abrupt), including the following: Dysphoric mood, irritability, agitation, dizziness, sensory
517 disturbances (e.g., paresthesias such as electric shock sensations and tinnitus), anxiety,
518 confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events
519 are generally self-limiting, there have been reports of serious discontinuation symptoms.

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

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

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

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

540 **Hyponatremia:** Hyponatremia may occur as a result of treatment with SSRIs and SNRIs,
541 including PAXIL CR. In many cases, this hyponatremia appears to be the result of the syndrome

542 of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than
543 110 mmol/L have been reported. Elderly patients may be at greater risk of developing
544 hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise
545 volume depleted may be at greater risk (see PRECAUTIONS: Geriatric Use). Discontinuation of
546 PAXIL CR should be considered in patients with symptomatic hyponatremia and appropriate
547 medical intervention should be instituted.

548 Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory
549 impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and
550 symptoms associated with more severe and/or acute cases have included hallucination, syncope,
551 seizure, coma, respiratory arrest, and death.

552 **Abnormal Bleeding:** SSRIs and SNRIs, including paroxetine, may increase the risk of
553 bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and
554 other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control
555 and cohort design) have demonstrated an association between use of drugs that interfere with
556 serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to
557 SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to
558 life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated
559 with the concomitant use of paroxetine and NSAIDs, aspirin, or other drugs that affect
560 coagulation.

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

568 **Use in Patients With Concomitant Illness:** Clinical experience with immediate-release
569 paroxetine hydrochloride in patients with certain concomitant systemic illness is limited. Caution
570 is advisable in using PAXIL CR in patients with diseases or conditions that could affect
571 metabolism or hemodynamic responses.

572 As with other SSRIs, mydriasis has been infrequently reported in premarketing studies with
573 paroxetine hydrochloride. A few cases of acute angle closure glaucoma associated with therapy
574 with immediate-release paroxetine have been reported in the literature. As mydriasis can cause
575 acute angle closure in patients with narrow angle glaucoma, caution should be used when
576 PAXIL CR is prescribed for patients with narrow angle glaucoma.

577 PAXIL CR or the immediate-release formulation has not been evaluated or used to any
578 appreciable extent in patients with a recent history of myocardial infarction or unstable heart
579 disease. Patients with these diagnoses were excluded from clinical studies during premarket
580 testing. Evaluation of electrocardiograms of 682 patients who received immediate-release
581 paroxetine hydrochloride in double-blind, placebo-controlled trials, however, did not indicate

582 that paroxetine is associated with the development of significant ECG abnormalities. Similarly,
583 paroxetine hydrochloride does not cause any clinically important changes in heart rate or blood
584 pressure.

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

588 **Information for Patients:** PAXIL CR should not be chewed or crushed, and should be
589 swallowed whole.

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

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

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

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

613 **Drugs That Interfere With Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin):**

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

618 **Interference With Cognitive and Motor Performance:** Any psychoactive drug may
619 impair judgment, thinking, or motor skills. Although in controlled studies immediate-release
620 paroxetine hydrochloride has not been shown to impair psychomotor performance, patients
621 should be cautioned about operating hazardous machinery, including automobiles, until they are

622 reasonably certain that therapy with PAXIL CR does not affect their ability to engage in such
623 activities.

624 **Completing Course of Therapy:** While patients may notice improvement with use of
625 PAXIL CR in 1 to 4 weeks, they should be advised to continue therapy as directed.

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

629 **Alcohol:** Although immediate-release paroxetine hydrochloride has not been shown to
630 increase the impairment of mental and motor skills caused by alcohol, patients should be advised
631 to avoid alcohol while taking PAXIL CR.

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

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

637 **Laboratory Tests:** There are no specific laboratory tests recommended.

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

644 **Monoamine Oxidase Inhibitors:** See CONTRAINDICATIONS and WARNINGS.

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

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

657 The concomitant use of PAXIL CR with MAOIs (including linezolid and intravenous
658 methylene blue) is contraindicated (see CONTRAINDICATIONS). The concomitant use of
659 PAXIL CR with other SSRIs, SNRIs or tryptophan is not recommended (see PRECAUTIONS:
660 Drug Interactions, *Tryptophan*).

661 **Thioridazine:** See CONTRAINDICATIONS and WARNINGS.

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

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

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

673 **Cimetidine:** Cimetidine inhibits many cytochrome P₄₅₀ (oxidative) enzymes. In a study
674 where immediate-release paroxetine (30 mg once daily) was dosed orally for 4 weeks,
675 steady-state plasma concentrations of paroxetine were increased by approximately 50% during
676 coadministration with oral cimetidine (300 mg three times daily) for the final week. Therefore,
677 when these drugs are administered concurrently, dosage adjustment of PAXIL CR after the
678 starting dose should be guided by clinical effect. The effect of paroxetine on cimetidine's
679 pharmacokinetics was not studied.

680 **Phenobarbital:** Phenobarbital induces many cytochrome P₄₅₀ (oxidative) enzymes. When a
681 single oral 30-mg dose of immediate-release paroxetine was administered at phenobarbital
682 steady state (100 mg once daily for 14 days), paroxetine AUC and T_{1/2} were reduced (by an
683 average of 25% and 38%, respectively) compared to paroxetine administered alone. The effect of
684 paroxetine on phenobarbital pharmacokinetics was not studied. Since paroxetine exhibits
685 nonlinear pharmacokinetics, the results of this study may not address the case where the 2 drugs
686 are both being chronically dosed. No initial dosage adjustment with PAXIL CR is considered
687 necessary when coadministered with phenobarbital; any subsequent adjustment should be guided
688 by clinical effect.

689 **Phenytoin:** When a single oral 30-mg dose of immediate-release paroxetine was
690 administered at phenytoin steady state (300 mg once daily for 14 days), paroxetine AUC and T_{1/2}
691 were reduced (by an average of 50% and 35%, respectively) compared to immediate-release
692 paroxetine administered alone. In a separate study, when a single oral 300-mg dose of phenytoin
693 was administered at paroxetine steady state (30 mg once daily for 14 days), phenytoin AUC was
694 slightly reduced (12% on average) compared to phenytoin administered alone. Since both drugs
695 exhibit nonlinear pharmacokinetics, the above studies may not address the case where the
696 2 drugs are both being chronically dosed. No initial dosage adjustments are considered necessary
697 when PAXIL CR is coadministered with phenytoin; any subsequent adjustments should be
698 guided by clinical effect (see ADVERSE REACTIONS: Postmarketing Reports).

699 **Drugs Metabolized by CYP2D6:** Many drugs, including most drugs effective in the
700 treatment of major depressive disorder (paroxetine, other SSRIs, and many tricyclics), are
701 metabolized by the cytochrome P₄₅₀ isozyme CYP2D6. Like other agents that are metabolized by

702 CYP2D6, paroxetine may significantly inhibit the activity of this isozyme. In most patients
703 (>90%), this CYP2D6 isozyme is saturated early during paroxetine dosing. In 1 study, daily
704 dosing of immediate-release paroxetine (20 mg once daily) under steady-state conditions
705 increased single-dose desipramine (100 mg) C_{max} , AUC, and $T_{1/2}$ by an average of approximately
706 2-, 5-, and 3-fold, respectively. Concomitant use of paroxetine with risperidone, a CYP2D6
707 substrate has also been evaluated. In 1 study, daily dosing of paroxetine 20 mg in patients
708 stabilized on risperidone (4 to 8 mg/day) increased mean plasma concentrations of risperidone
709 approximately 4-fold, decreased 9-hydroxyrisperidone concentrations approximately 10%, and
710 increased concentrations of the active moiety (the sum of risperidone plus 9-hydroxyrisperidone)
711 approximately 1.4-fold. The effect of paroxetine on the pharmacokinetics of atomoxetine has
712 been evaluated when both drugs were at steady state. In healthy volunteers who were extensive
713 metabolizers of CYP2D6, paroxetine 20 mg daily was given in combination with 20 mg
714 atomoxetine every 12 hours. This resulted in increases in steady state atomoxetine AUC values
715 that were 6- to 8-fold greater and in atomoxetine C_{max} values that were 3- to 4-fold greater than
716 when atomoxetine was given alone. Dosage adjustment of atomoxetine may be necessary and it
717 is recommended that atomoxetine be initiated at a reduced dose when given with paroxetine.

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

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

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

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

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

735 **Drugs Metabolized by Cytochrome CYP3A4:** An in vivo interaction study involving
736 the coadministration under steady-state conditions of paroxetine and terfenadine, a substrate for
737 CYP3A4, revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, in vitro
738 studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times
739 more potent than paroxetine as an inhibitor of the metabolism of several substrates for this
740 enzyme, including terfenadine, astemizole, cisapride, triazolam, and cyclosporine. Based on the
741 assumption that the relationship between paroxetine's in vitro K_i and its lack of effect on

742 terfenadine's in vivo clearance predicts its effect on other CYP3A4 substrates, paroxetine's
743 extent of inhibition of CYP3A4 activity is not likely to be of clinical significance.

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

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

754 **Drugs That Interfere With Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin):**
755 Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of
756 the case-control and cohort design that have demonstrated an association between use of
757 psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper
758 gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may
759 potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have
760 been reported when SSRIs or SNRIs are coadministered with warfarin. Patients receiving
761 warfarin therapy should be carefully monitored when paroxetine is initiated or discontinued.

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

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

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

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

774 **Procyclidine:** Daily oral dosing of immediate-release paroxetine (30 mg once daily)
775 increased steady-state AUC₀₋₂₄, C_{max}, and C_{min} values of procyclidine (5 mg oral once daily) by
776 35%, 37%, and 67%, respectively, compared to procyclidine alone at steady state. If
777 anticholinergic effects are seen, the dose of procyclidine should be reduced.

778 **Beta-Blockers:** In a study where propranolol (80 mg twice daily) was dosed orally for
779 18 days, the established steady-state plasma concentrations of propranolol were unaltered during
780 coadministration with immediate-release paroxetine (30 mg once daily) for the final 10 days. The
781 effects of propranolol on paroxetine have not been evaluated (see ADVERSE REACTIONS:

782 Postmarketing Reports).

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

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

790 **Electroconvulsive Therapy (ECT):** There are no clinical studies of the combined use of
791 ECT and PAXIL CR.

792 **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** Two-year
793 carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and
794 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to approximately 2
795 (mouse) and 3 (rat) times the MRHD on a mg/m² basis. There was a significantly greater number
796 of male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50, and 4/50 for
797 control, low-, middle-, and high-dose groups, respectively) and a significantly increased linear
798 trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats
799 were not affected. Although there was a dose-related increase in the number of tumors in mice,
800 there was no drug-related increase in the number of mice with tumors. The relevance of these
801 findings to humans is unknown.

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

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

809 A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of
810 15 mg/kg/day, which is approximately twice the MRHD on a mg/m² basis. Irreversible lesions
811 occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks.
812 These lesions consisted of vacuolation of epididymal tubular epithelium at 50 mg/kg/day and
813 atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis at
814 25 mg/kg/day (approximately 8 and 4 times the MRHD on a mg/m² basis).

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

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

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

820 **Pediatric Use:** Safety and effectiveness in the pediatric population have not been established
821 (see BOX WARNING and WARNINGS: Clinical Worsening and Suicide Risk). Three placebo-

822 controlled trials in 752 pediatric patients with MDD have been conducted with immediate-
823 release PAXIL, and the data were not sufficient to support a claim for use in pediatric patients.
824 Anyone considering the use of PAXIL CR in a child or adolescent must balance the potential
825 risks with the clinical need. Decreased appetite and weight loss have been observed in association
826 with the use of SSRIs. Consequently, regular monitoring of weight and growth should be performed
827 in children and adolescents treated with an SSRI such as PAXIL CR.

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

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

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

843 In worldwide premarketing clinical trials with immediate-release paroxetine hydrochloride,
844 17% of paroxetine-treated patients (approximately 700) were 65 years or older. Pharmacokinetic
845 studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended;
846 there were, however, no overall differences in the adverse event profile between elderly and
847 younger patients, and effectiveness was similar in younger and older patients (see CLINICAL
848 PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

849 In a controlled study focusing specifically on elderly patients with major depressive disorder,
850 PAXIL CR was demonstrated to be safe and effective in the treatment of elderly patients (>60
851 years) with major depressive disorder (see CLINICAL PHARMACOLOGY: Clinical Trials and
852 ADVERSE REACTIONS: Table 3.)

853 **ADVERSE REACTIONS**

854 The information included under the “Adverse Findings Observed in Short-Term,
855 Placebo-Controlled Trials With PAXIL CR” subsection of ADVERSE REACTIONS is based on
856 data from 11 placebo-controlled clinical trials. Three of these studies were conducted in patients
857 with major depressive disorder, 3 studies were done in patients with panic disorder, 1 study was
858 conducted in patients with social anxiety disorder, and 4 studies were done in female patients
859 with PMDD. Two of the studies in major depressive disorder, which enrolled patients in the age
860 range 18 to 65 years, are pooled. Information from a third study of major depressive disorder,

861 which focused on elderly patients (60 to 88 years), is presented separately as is the information
862 from the panic disorder studies and the information from the PMDD studies. Information on
863 additional adverse events associated with PAXIL CR and the immediate-release formulation of
864 paroxetine hydrochloride is included in a separate subsection (see Other Events Observed During
865 the Clinical Development of Paroxetine).

866 **Adverse Findings Observed in Short-Term, Placebo-Controlled Trials With PAXIL**
867 **CR:**

868 **Adverse Events Associated With Discontinuation of Treatment: *Major Depressive***
869 ***Disorder*:** Ten percent (21/212) of patients treated with PAXIL CR discontinued treatment due
870 to an adverse event in a pool of 2 studies of patients with major depressive disorder. The most
871 common events ($\geq 1\%$) associated with discontinuation and considered to be drug related (i.e.,
872 those events associated with dropout at a rate approximately twice or greater for PAXIL CR
873 compared to placebo) included the following:

	PAXIL CR (n = 212)	Placebo (n = 211)
Nausea	3.7%	0.5%
Asthenia	1.9%	0.5%
Dizziness	1.4%	0.0%
Somnolence	1.4%	0.0%

874
875 In a placebo-controlled study of elderly patients with major depressive disorder, 13% (13/104)
876 of patients treated with PAXIL CR discontinued due to an adverse event. Events meeting the
877 above criteria included the following:

	PAXIL CR (n = 104)	Placebo (n = 109)
Nausea	2.9%	0.0%
Headache	1.9%	0.9%
Depression	1.9%	0.0%
LFT's abnormal	1.9%	0.0%

878
879 ***Panic Disorder*:** Eleven percent (50/444) of patients treated with PAXIL CR in panic
880 disorder studies discontinued treatment due to an adverse event. Events meeting the above
881 criteria included the following:

	PAXIL CR (n = 444)	Placebo (n = 445)
Nausea	2.9%	0.4%
Insomnia	1.8%	0.0%
Headache	1.4%	0.2%
Asthenia	1.1%	0.0%

882

883 **Social Anxiety Disorder:** Three percent (5/186) of patients treated with PAXIL CR in the
884 social anxiety disorder study discontinued treatment due to an adverse event. Events meeting the
885 above criteria included the following:

	PAXIL CR (n = 186)	Placebo (n = 184)
Nausea	2.2%	0.5%
Headache	1.6%	0.5%
Diarrhea	1.1%	0.5%

886

887 **Premenstrual Dysphoric Disorder:** Spontaneously reported adverse events were
888 monitored in studies of both continuous and intermittent dosing of PAXIL CR in the treatment of
889 PMDD. Generally, there were few differences in the adverse event profiles of the 2 dosing
890 regimens. Thirteen percent (88/681) of patients treated with PAXIL CR in PMDD studies of
891 continuous dosing discontinued treatment due to an adverse event.

892 The most common events ($\geq 1\%$) associated with discontinuation in either group treated with
893 PAXIL CR with an incidence rate that is at least twice that of placebo in PMDD trials that
894 employed a continuous dosing regimen are shown in the following table. This table also shows
895 those events that were dose dependent (indicated with an asterisk) as defined as events having an
896 incidence rate with 25 mg of PAXIL CR that was at least twice that with 12.5 mg of PAXIL CR
897 (as well as the placebo group).

	PAXIL CR 25 mg (n = 348)	PAXIL CR 12.5 mg (n = 333)	Placebo (n = 349)
TOTAL	15%	9.9%	6.3%
Nausea ^a	6.0%	2.4%	0.9%
Asthenia	4.9%	3.0%	1.4%
Somnolence ^a	4.3%	1.8%	0.3%
Insomnia	2.3%	1.5%	0.0%
Concentration Impaired ^a	2.0%	0.6%	0.3%
Dry mouth ^a	2.0%	0.6%	0.3%
Dizziness ^a	1.7%	0.6%	0.6%
Decreased Appetite ^a	1.4%	0.6%	0.0%
Sweating ^a	1.4%	0.0%	0.3%
Tremor ^a	1.4%	0.3%	0.0%
Yawn ^a	1.1%	0.0%	0.0%
Diarrhea	0.9%	1.2%	0.0%

898 a. Events considered to be dose dependent are defined as events having an incidence rate with
899 25 mg of PAXIL CR that was at least twice that with 12.5 mg of PAXIL CR (as well as the
900 placebo group).
901

902 **Commonly Observed Adverse Events: Major Depressive Disorder:** The most
903 commonly observed adverse events associated with the use of PAXIL CR in a pool of 2 trials
904 (incidence of 5.0% or greater and incidence for PAXIL CR at least twice that for placebo,
905 derived from Table 2) were: Abnormal ejaculation, abnormal vision, constipation, decreased
906 libido, diarrhea, dizziness, female genital disorders, nausea, somnolence, sweating, trauma,
907 tremor, and yawning.

908 Using the same criteria, the adverse events associated with the use of PAXIL CR in a study of
909 elderly patients with major depressive disorder were: Abnormal ejaculation, constipation,
910 decreased appetite, dry mouth, impotence, infection, libido decreased, sweating, and tremor.

911 **Panic Disorder:** In the pool of panic disorder studies, the adverse events meeting these
912 criteria were: Abnormal ejaculation, somnolence, impotence, libido decreased, tremor, sweating,
913 and female genital disorders (generally anorgasmia or difficulty achieving orgasm).

914 **Social Anxiety Disorder:** In the social anxiety disorder study, the adverse events meeting
915 these criteria were: Nausea, asthenia, abnormal ejaculation, sweating, somnolence, impotence,
916 insomnia, and libido decreased.

917 **Premenstrual Dysphoric Disorder:** The most commonly observed adverse events
918 associated with the use of PAXIL CR either during continuous dosing or luteal phase dosing
919 (incidence of 5% or greater and incidence for PAXIL CR at least twice that for placebo, derived
920 from Table 6) were: Nausea, asthenia, libido decreased, somnolence, insomnia, female genital
921 disorders, sweating, dizziness, diarrhea, and constipation.

922 In the luteal phase dosing PMDD trial, which employed dosing of 12.5 mg/day or 25 mg/day

923 of PAXIL CR limited to the 2 weeks prior to the onset of menses over 3 consecutive menstrual
924 cycles, adverse events were evaluated during the first 14 days of each off-drug phase. When the
925 3 off-drug phases were combined, the following adverse events were reported at an incidence of
926 2% or greater for PAXIL CR and were at least twice the rate of that reported for placebo:
927 Infection (5.3% versus 2.5%), depression (2.8% versus 0.8%), insomnia (2.4% versus 0.8%),
928 sinusitis (2.4% versus 0%), and asthenia (2.0% versus 0.8%).

929 **Incidence in Controlled Clinical Trials:** Table 2 enumerates adverse events that occurred at
930 an incidence of 1% or more among patients treated with PAXIL CR, aged 18 to 65, who
931 participated in 2 short-term (12-week) placebo-controlled trials in major depressive disorder in
932 which patients were dosed in a range of 25 mg to 62.5 mg/day. Table 3 enumerates adverse
933 events reported at an incidence of 5% or greater among elderly patients (ages 60 to 88) treated
934 with PAXIL CR who participated in a short-term (12-week) placebo-controlled trial in major
935 depressive disorder in which patients were dosed in a range of 12.5 mg to 50 mg/day. Table 4
936 enumerates adverse events reported at an incidence of 1% or greater among patients (19 to 72
937 years) treated with PAXIL CR who participated in short-term (10-week) placebo-controlled trials
938 in panic disorder in which patients were dosed in a range of 12.5 mg to 75 mg/day. Table 5
939 enumerates adverse events reported at an incidence of 1% or greater among adult patients treated
940 with PAXIL CR who participated in a short-term (12-week), double-blind, placebo-controlled
941 trial in social anxiety disorder in which patients were dosed in a range of 12.5 to 37.5 mg/day.
942 Table 6 enumerates adverse events that occurred at an incidence of 1% or more among patients
943 treated with PAXIL CR who participated in three, 12-week, placebo-controlled trials in PMDD
944 in which patients were dosed at 12.5 mg/day or 25 mg/day and in one 12-week
945 placebo-controlled trial in which patients were dosed for 2 weeks prior to the onset of menses
946 (luteal phase dosing) at 12.5 mg/day or 25 mg/day. Reported adverse events were classified
947 using a standard COSTART-based Dictionary terminology.

948 The prescriber should be aware that these figures cannot be used to predict the incidence of
949 side effects in the course of usual medical practice where patient characteristics and other factors
950 differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be
951 compared with figures obtained from other clinical investigations involving different treatments,
952 uses, and investigators. The cited figures, however, do provide the prescribing physician with
953 some basis for estimating the relative contribution of drug and nondrug factors to the side effect
954 incidence rate in the population studied.

955

956
957
958

Table 2. Treatment-Emergent Adverse Events Occurring in $\geq 1\%$ of Patients Treated With PAXIL CR in a Pool of 2 Studies in Major Depressive Disorder^{a,b}

Body System/Adverse Event	% Reporting Event	
	PAXIL CR (n = 212)	Placebo (n = 211)
Body as a Whole		
Headache	27%	20%
Asthenia	14%	9%
Infection ^c	8%	5%
Abdominal Pain	7%	4%
Back Pain	5%	3%
Trauma ^d	5%	1%
Pain ^e	3%	1%
Allergic Reaction ^f	2%	1%
Cardiovascular System		
Tachycardia	1%	0%
Vasodilatation ^g	2%	0%
Digestive System		
Nausea	22%	10%
Diarrhea	18%	7%
Dry Mouth	15%	8%
Constipation	10%	4%
Flatulence	6%	4%
Decreased Appetite	4%	2%
Vomiting	2%	1%
Nervous System		
Somnolence	22%	8%
Insomnia	17%	9%
Dizziness	14%	4%
Libido Decreased	7%	3%
Tremor	7%	1%
Hypertonia	3%	1%
Paresthesia	3%	1%
Agitation	2%	1%
Confusion	1%	0%
Respiratory System		
Yawn	5%	0%
Rhinitis	4%	1%
Cough Increased	2%	1%
Bronchitis	1%	0%

959

Skin and Appendages		
Sweating	6%	2%
Photosensitivity	2%	0%
Special Senses		
Abnormal Vision ^h	5%	1%
Taste Perversion	2%	0%
Urogenital System		
Abnormal Ejaculation ^{i,j}	26%	1%
Female Genital Disorder ^{i,k}	10%	<1%
Impotence ⁱ	5%	3%
Urinary Tract Infection	3%	1%
Menstrual Disorder ⁱ	2%	<1%
Vaginitis ⁱ	2%	0%

- 961 a. Adverse events for which the PAXIL CR reporting incidence was less than or equal to the
962 placebo incidence are not included. These events are: Abnormal dreams, anxiety, arthralgia,
963 depersonalization, dysmenorrhea, dyspepsia, hyperkinesia, increased appetite, myalgia,
964 nervousness, pharyngitis, purpura, rash, respiratory disorder, sinusitis, urinary frequency, and
965 weight gain.
- 966 b. <1% means greater than zero and less than 1%.
- 967 c. Mostly flu.
- 968 d. A wide variety of injuries with no obvious pattern.
- 969 e. Pain in a variety of locations with no obvious pattern.
- 970 f. Most frequently seasonal allergic symptoms.
- 971 g. Usually flushing.
- 972 h. Mostly blurred vision.
- 973 i. Based on the number of males or females.
- 974 j. Mostly anorgasmia or delayed ejaculation.
- 975 k. Mostly anorgasmia or delayed orgasm.

976

977
978
979
980

Table 3. Treatment-Emergent Adverse Events Occurring in $\geq 5\%$ of Patients Treated With PAXIL CR in a Study of Elderly Patients With Major Depressive Disorder^{a,b}

Body System/Adverse Event	% Reporting Event	
	PAXIL CR (n = 104)	Placebo (n = 109)
Body as a Whole		
Headache	17%	13%
Asthenia	15%	14%
Trauma	8%	5%
Infection	6%	2%
Digestive System		
Dry Mouth	18%	7%
Diarrhea	15%	9%
Constipation	13%	5%
Dyspepsia	13%	10%
Decreased Appetite	12%	5%
Flatulence	8%	7%
Nervous System		
Somnolence	21%	12%
Insomnia	10%	8%
Dizziness	9%	5%
Libido Decreased	8%	<1%
Tremor	7%	0%
Skin and Appendages		
Sweating	10%	<1%
Urogenital System		
Abnormal Ejaculation ^{c,d}	17%	3%
Impotence ^c	9%	3%

981 a. Adverse events for which the PAXIL CR reporting incidence was less than or equal to the
982 placebo incidence are not included. These events are nausea and respiratory disorder.
983 b. <1% means greater than zero and less than 1%.
984 c. Based on the number of males.
985 d. Mostly anorgasmia or delayed ejaculation.
986

987 **Table 4. Treatment-Emergent Adverse Events Occurring in ≥1% of Patients Treated With**
 988 **PAXIL CR in a Pool of 3 Panic Disorder Studies^{a,b}**

Body System/Adverse Event	% Reporting Event	
	PAXIL CR (n = 444)	Placebo (n = 445)
Body as a Whole		
Asthenia	15%	10%
Abdominal Pain	6%	4%
Trauma ^c	5%	4%
Cardiovascular System		
Vasodilation ^d	3%	2%
Digestive System		
Nausea	23%	17%
Dry Mouth	13%	9%
Diarrhea	12%	9%
Constipation	9%	6%
Decreased Appetite	8%	6%
Metabolic/Nutritional Disorders		
Weight Loss	1%	0%
Musculoskeletal System		
Myalgia	5%	3%
Nervous System		
Insomnia	20%	11%
Somnolence	20%	9%
Libido Decreased	9%	4%
Nervousness	8%	7%
Tremor	8%	2%
Anxiety	5%	4%
Agitation	3%	2%
Hypertonia ^e	2%	<1%
Myoclonus	2%	<1%
Respiratory System		
Sinusitis	8%	5%
Yawn	3%	0%
Skin and Appendages		
Sweating	7%	2%
Special Senses		
Abnormal Vision ^f	3%	<1%
Urogenital System		
Abnormal Ejaculation ^{g,h}	27%	3%
Impotence ^g	10%	1%
Female Genital Disorders ^{i,j}	7%	1%
Urinary Frequency	2%	<1%
Urination Impaired	2%	<1%
Vaginitis ⁱ	1%	<1%

- 989 a. Adverse events for which the reporting rate for PAXIL CR was less than or equal to the
990 placebo rate are not included. These events are: Abnormal dreams, allergic reaction, back
991 pain, bronchitis, chest pain, concentration impaired, confusion, cough increased, depression,
992 dizziness, dysmenorrhea, dyspepsia, fever, flatulence, headache, increased appetite, infection,
993 menstrual disorder, migraine, pain, paresthesia, pharyngitis, respiratory disorder, rhinitis,
994 tachycardia, taste perversion, thinking abnormal, urinary tract infection, and vomiting.
995 b. <1% means greater than zero and less than 1%.
996 c. Various physical injuries.
997 d. Mostly flushing.
998 e. Mostly muscle tightness or stiffness.
999 f. Mostly blurred vision.
1000 g. Based on the number of male patients.
1001 h. Mostly anorgasmia or delayed ejaculation.
1002 i. Based on the number of female patients.
1003 j. Mostly anorgasmia or difficulty achieving orgasm.
1004

1005 **Table 5. Treatment-Emergent Adverse Effects Occurring in ≥1% of Patients Treated**
1006 **With PAXIL CR in a Social Anxiety Disorder Study^{a,b}**

Body System/Adverse Event	% Reporting Event	
	PAXIL CR (n = 186)	Placebo (n = 184)
Body as a Whole		
Headache	23%	17%
Asthenia	18%	7%
Abdominal Pain	5%	4%
Back Pain	4%	1%
Trauma ^c	3%	<1%
Allergic Reaction ^d	2%	<1%
Chest Pain	1%	<1%
Cardiovascular System		
Hypertension	2%	0%
Migraine	2%	1%
Tachycardia	2%	1%
Digestive System		
Nausea	22%	6%
Diarrhea	9%	8%
Constipation	5%	2%
Dry Mouth	3%	2%
Dyspepsia	2%	<1%
Decreased Appetite	1%	<1%

Tooth Disorder	1%	0%
Metabolic/Nutritional Disorders		
Weight Gain	3%	1%
Weight Loss	1%	0%
Nervous System		
Insomnia	9%	4%
Somnolence	9%	4%
Libido Decreased	8%	1%
Dizziness	7%	4%
Tremor	4%	2%
Anxiety	2%	1%
Concentration Impaired	2%	0%
Depression	2%	1%
Myoclonus	1%	<1%
Paresthesia	1%	<1%
Respiratory System		
Yawn	2%	0%
Skin and Appendages		
Sweating	14%	3%
Eczema	1%	0%
Special Senses		
Abnormal Vision ^e	2%	0%
Abnormality of Accommodation	2%	0%
Urogenital System		
Abnormal Ejaculation ^{f,g}	15%	1%
Impotence ^f	9%	0%
Female Genital Disorders ^{h,i}	3%	0%

- 1007 a. Adverse events for which the reporting rate for PAXIL CR was less than or equal to the
1008 placebo rate are not included. These events are: Dysmenorrhea, flatulence, gastroenteritis,
1009 hypertonia, infection, pain, pharyngitis, rash, respiratory disorder, rhinitis, and vomiting.
1010 b. <1% means greater than zero and less than 1%.
1011 c. Various physical injuries.
1012 d. Most frequently seasonal allergic symptoms.
1013 e. Mostly blurred vision.
1014 f. Based on the number of male patients.
1015 g. Mostly anorgasmia or delayed ejaculation.
1016 h. Based on the number of female patients.
1017 i. Mostly anorgasmia or difficulty achieving orgasm.

1018
 1019 **Table 6. Treatment-Emergent Adverse Events Occurring in ≥1% of Patients Treated With**
 1020 **PAXIL CR in a Pool of 3 Premenstrual Dysphoric Disorder Studies With Continuous**
 1021 **Dosing or in 1 Premenstrual Dysphoric Disorder Study With Luteal Phase Dosing^{a,b,c}**

Body System/Adverse Event	% Reporting Event			
	Continuous Dosing		Luteal Phase Dosing	
	PAXIL CR (n = 681)	Placebo (n = 349)	PAXIL CR (n = 246)	Placebo (n = 120)
Body as a Whole				
Asthenia	17%	6%	15%	4%
Headache	15%	12%	-	-
Infection	6%	4%	-	-
Abdominal pain	-	-	3%	0%
Cardiovascular System				
Migraine	1%	<1%	-	-
Digestive System				
Nausea	17%	7%	18%	2%
Diarrhea	6%	2%	6%	0%
Constipation	5%	1%	2%	<1%
Dry Mouth	4%	2%	2%	<1%
Increased Appetite	3%	<1%	-	-
Decreased Appetite	2%	<1%	2%	0%
Dyspepsia	2%	1%	2%	2%
Gingivitis	-	-	1%	0%
Metabolic and Nutritional Disorders				
Generalized Edema	-	-	1%	<1%
Weight Gain	-	-	1%	<1%
Musculoskeletal System				
Arthralgia	2%	1%	-	-
Nervous System				
Libido Decreased	12%	5%	9%	6%
Somnolence	9%	2%	3%	<1%
Insomnia	8%	2%	7%	3%
Dizziness	7%	3%	6%	3%
Tremor	4%	<1%	5%	0%
Concentration Impaired	3%	<1%	1%	0%
Nervousness	2%	<1%	3%	2%
Anxiety	2%	1%	-	-

Lack of Emotion	2%	<1%	-	-
Depression	-	-	2%	<1%
Vertigo	-	-	2%	<1%
Abnormal Dreams	1%	<1%	-	-
Amnesia	-	-	1%	0%
Respiratory System				
Sinusitis	-	-	4%	2%
Yawn	2%	<1%	-	-
Bronchitis	-	-	2%	0%
Cough Increased	1%	<1%	-	-
Skin and Appendages				
Sweating	7%	<1%	6%	<1%
Special Senses				
Abnormal Vision	-	-	1%	0%
Urogenital System				
Female Genital Disorders ^d	8%	1%	2%	0%
Menorrhagia	1%	<1%	-	-
Vaginal Moniliasis	1%	<1%	-	-
Menstrual Disorder	-	-	1%	0%

- 1022 a. Adverse events for which the reporting rate of PAXIL CR was less than or equal to the
1023 placebo rate are not included. These events for continuous dosing are: Abdominal pain, back
1024 pain, pain, trauma, weight gain, myalgia, pharyngitis, respiratory disorder, rhinitis, sinusitis,
1025 pruritis, dysmenorrhea, menstrual disorder, urinary tract infection, and vomiting. The events
1026 for luteal phase dosing are: Allergic reaction, back pain, headache, infection, pain, trauma,
1027 myalgia, anxiety, pharyngitis, respiratory disorder, cystitis, and dysmenorrhea.
- 1028 b. <1% means greater than zero and less than 1%.
- 1029 c. The luteal phase and continuous dosing PMDD trials were not designed for making direct
1030 comparisons between the 2 dosing regimens. Therefore, a comparison between the 2 dosing
1031 regimens of the PMDD trials of incidence rates shown in Table 6 should be avoided.
- 1032 d. Mostly anorgasmia or difficulty achieving orgasm.

1033

1034 **Dose Dependency of Adverse Events:** Table 7 shows results in PMDD trials of
1035 common adverse events, defined as events with an incidence of $\geq 1\%$ with 25 mg of PAXIL CR
1036 that was at least twice that with 12.5 mg of PAXIL CR and with placebo.
1037

1038 **Table 7. Incidence of Common Adverse Events in Placebo, 12.5 mg, and 25 mg of**
 1039 **PAXIL CR in a Pool of 3 Fixed-Dose PMDD Trials**

	PAXIL CR 25 mg (n = 348)	PAXIL CR 12.5 mg (n = 333)	Placebo (n = 349)
Common Adverse Event			
Sweating	8.9%	4.2%	0.9%
Tremor	6.0%	1.5%	0.3%
Concentration Impaired	4.3%	1.5%	0.6%
Yawn	3.2%	0.9%	0.3%
Paresthesia	1.4%	0.3%	0.3%
Hyperkinesia	1.1%	0.3%	0.0%
Vaginitis	1.1%	0.3%	0.3%

1040
 1041 A comparison of adverse event rates in a fixed-dose study comparing immediate-release
 1042 paroxetine with placebo in the treatment of major depressive disorder revealed a clear dose
 1043 dependency for some of the more common adverse events associated with the use of
 1044 immediate-release paroxetine.

1045 **Male and Female Sexual Dysfunction With SSRIs:** Although changes in sexual desire,
 1046 sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric
 1047 disorder, they may also be a consequence of pharmacologic treatment. In particular, some
 1048 evidence suggests that SSRIs can cause such untoward sexual experiences.

1049 Reliable estimates of the incidence and severity of untoward experiences involving sexual
 1050 desire, performance, and satisfaction are difficult to obtain; however, in part because patients and
 1051 physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of
 1052 untoward sexual experience and performance cited in product labeling, are likely to
 1053 underestimate their actual incidence.

1054 The percentage of patients reporting symptoms of sexual dysfunction in the pool of 2
 1055 placebo-controlled trials in nonelderly patients with major depressive disorder, in the pool of 3
 1056 placebo-controlled trials in patients with panic disorder, in the placebo-controlled trial in patients
 1057 with social anxiety disorder, and in the intermittent dosing and the pool of 3 placebo-controlled
 1058 continuous dosing trials in female patients with PMDD are as follows:

1059

	Major Depressive Disorder		Panic Disorder		Social Anxiety Disorder		PMDD Continuous Dosing		PMDD Luteal Phase Dosing	
	PAXIL CR	Placebo	PAXIL CR	Placebo	PAXIL CR	Placebo	PAXIL CR	Placebo	PAXIL CR	Placebo
n (males)	78	78	162	194	88	97	n/a	n/a	n/a	n/a
Decreased Libido	10%	5%	9%	6%	13%	1%	n/a	n/a	n/a	n/a
Ejaculatory Disturbance	26%	1%	27%	3%	15%	1%	n/a	n/a	n/a	n/a
Impotence	5%	3%	10%	1%	9%	0%	n/a	n/a	n/a	n/a
n (females)	134	133	282	251	98	87	681	349	246	120
Decreased Libido	4%	2%	8%	2%	4%	1%	12%	5%	9%	6%
Orgasmic Disturbance	10%	<1%	7%	1%	3%	0%	8%	1%	2%	0%

1060

1061 There are no adequate, controlled studies examining sexual dysfunction with paroxetine
1062 treatment.

1063 Paroxetine treatment has been associated with several cases of priapism. In those cases with a
1064 known outcome, patients recovered without sequelae.

1065 While it is difficult to know the precise risk of sexual dysfunction associated with the use of
1066 SSRIs, physicians should routinely inquire about such possible side effects.

1067 **Weight and Vital Sign Changes:** Significant weight loss may be an undesirable result of
1068 treatment with paroxetine for some patients but, on average, patients in controlled trials with
1069 PAXIL CR or the immediate-release formulation, had minimal weight loss (about 1 pound). No
1070 significant changes in vital signs (systolic and diastolic blood pressure, pulse, and temperature)
1071 were observed in patients treated with PAXIL CR, or immediate-release paroxetine
1072 hydrochloride, in controlled clinical trials.

1073 **ECG Changes:** In an analysis of ECGs obtained in 682 patients treated with
1074 immediate-release paroxetine and 415 patients treated with placebo in controlled clinical trials,
1075 no clinically significant changes were seen in the ECGs of either group.

1076 **Liver Function Tests:** In a pool of 2 placebo-controlled clinical trials, patients treated with
1077 PAXIL CR or placebo exhibited abnormal values on liver function tests at comparable rates. In
1078 particular, the controlled-release paroxetine-versus-placebo comparisons for alkaline
1079 phosphatase, SGOT, SGPT, and bilirubin revealed no differences in the percentage of patients
1080 with marked abnormalities.

1081 In a study of elderly patients with major depressive disorder, 3 of 104 patients treated with
1082 PAXIL CR and none of 109 placebo patients experienced liver transaminase elevations of
1083 potential clinical concern.

1084 Two of the patients treated with PAXIL CR dropped out of the study due to abnormal liver
1085 function tests; the third patient experienced normalization of transaminase levels with continued
1086 treatment. Also, in the pool of 3 studies of patients with panic disorder, 4 of 444 patients treated
1087 with PAXIL CR and none of 445 placebo patients experienced liver transaminase elevations of
1088 potential clinical concern. Elevations in all 4 patients decreased substantially after
1089 discontinuation of PAXIL CR. The clinical significance of these findings is unknown.

1090 In placebo-controlled clinical trials with the immediate-release formulation of paroxetine,
1091 patients exhibited abnormal values on liver function tests at no greater rate than that seen in
1092 placebo-treated patients.

1093 **Hallucinations:** In pooled clinical trials of immediate-release paroxetine hydrochloride,
1094 hallucinations were observed in 22 of 9,089 patients receiving drug and in 4 of 3,187 patients
1095 receiving placebo.

1096 **Other Events Observed During the Clinical Development of Paroxetine:** The
1097 following adverse events were reported during the clinical development of PAXIL CR and/or the
1098 clinical development of the immediate-release formulation of paroxetine.

1099 Adverse events for which frequencies are provided below occurred in clinical trials with the
1100 controlled-release formulation of paroxetine. During its premarketing assessment in major
1101 depressive disorder, panic disorder, social anxiety disorder, and PMDD, multiple doses of
1102 PAXIL CR were administered to 1,627 patients in phase 3 double-blind, controlled, outpatient
1103 studies. Untoward events associated with this exposure were recorded by clinical investigators
1104 using terminology of their own choosing. Consequently, it is not possible to provide a
1105 meaningful estimate of the proportion of individuals experiencing adverse events without first
1106 grouping similar types of untoward events into a smaller number of standardized event
1107 categories.

1108 In the tabulations that follow, reported adverse events were classified using a
1109 COSTART-based dictionary. The frequencies presented, therefore, represent the proportion of
1110 the 1,627 patients exposed to PAXIL CR who experienced an event of the type cited on at least 1
1111 occasion while receiving PAXIL CR. All reported events are included except those already listed
1112 in Tables 2 through 7 and those events where a drug cause was remote. If the COSTART term
1113 for an event was so general as to be uninformative, it was deleted or, when possible, replaced
1114 with a more informative term. It is important to emphasize that although the events reported
1115 occurred during treatment with paroxetine, they were not necessarily caused by it.

1116 Events are further categorized by body system and listed in order of decreasing frequency
1117 according to the following definitions: Frequent adverse events are those occurring on 1 or more
1118 occasions in at least 1/100 patients (only those not already listed in the tabulated results from
1119 placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in
1120 1/100 to 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients.

1121 Adverse events for which frequencies are not provided occurred during the premarketing
1122 assessment of immediate-release paroxetine in phase 2 and 3 studies of major depressive
1123 disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized

1124 anxiety disorder, and posttraumatic stress disorder. The conditions and duration of exposure to
1125 immediate-release paroxetine varied greatly and included (in overlapping categories) open and
1126 double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and
1127 fixed-dose and titration studies. Only those events not previously listed for controlled-release
1128 paroxetine are included. The extent to which these events may be associated with PAXIL CR is
1129 unknown.

1130 Events are listed alphabetically within the respective body system. Events of major clinical
1131 importance are also described in the PRECAUTIONS section.

1132 **Body as a Whole:** Infrequent were chills, face edema, fever, flu syndrome, malaise; rare
1133 were abscess, anaphylactoid reaction, anticholinergic syndrome, hypothermia; also observed
1134 were adrenergic syndrome, neck rigidity, sepsis.

1135 **Cardiovascular System:** Infrequent were angina pectoris, bradycardia, hematoma,
1136 hypertension, hypotension, palpitation, postural hypotension, supraventricular tachycardia,
1137 syncope; rare were bundle branch block; also observed were arrhythmia nodal, atrial fibrillation,
1138 cerebrovascular accident, congestive heart failure, low cardiac output, myocardial infarct,
1139 myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles,
1140 thrombophlebitis, thrombosis, vascular headache, ventricular extrasystoles.

1141 **Digestive System:** Infrequent were bruxism, dysphagia, eructation, gastritis,
1142 gastroenteritis, gastroesophageal reflux, gingivitis, hemorrhoids, liver function test abnormal,
1143 melena, pancreatitis, rectal hemorrhage, toothache, ulcerative stomatitis; rare were colitis,
1144 glossitis, gum hyperplasia, hepatosplenomegaly, increased salivation, intestinal obstruction,
1145 peptic ulcer, stomach ulcer, throat tightness; also observed were aphthous stomatitis, bloody
1146 diarrhea, bulimia, cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions,
1147 fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, jaundice, mouth
1148 ulceration, salivary gland enlargement, sialadenitis, stomatitis, tongue discoloration, tongue
1149 edema.

1150 **Endocrine System:** Infrequent were ovarian cyst, testes pain; rare were diabetes mellitus,
1151 hyperthyroidism; also observed were goiter, hypothyroidism, thyroiditis.

1152 **Hemic and Lymphatic System:** Infrequent were anemia, eosinophilia, hypochromic
1153 anemia, leukocytosis, leukopenia, lymphadenopathy, purpura; rare were thrombocytopenia; also
1154 observed were anisocytosis, basophilia, bleeding time increased, lymphedema, lymphocytosis,
1155 lymphopenia, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia.

1156 **Metabolic and Nutritional Disorders:** Infrequent were generalized edema,
1157 hyperglycemia, hypokalemia, peripheral edema, SGOT increased, SGPT increased, thirst; rare
1158 were bilirubinemia, dehydration, hyperkalemia, obesity; also observed were alkaline phosphatase
1159 increased, BUN increased, creatinine phosphokinase increased, gamma globulins increased,
1160 gout, hypercalcemia, hypercholesteremia, hyperphosphatemia, hypocalcemia, hypoglycemia,
1161 hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased.

1162 **Musculoskeletal System:** Infrequent were arthritis, bursitis, tendonitis; rare were
1163 myasthenia, myopathy, myositis; also observed were generalized spasm, osteoporosis,

1164 tenosynovitis, tetany.

1165 **Nervous System:** Frequent were depression; infrequent were amnesia, convulsion,
1166 depersonalization, dystonia, emotional lability, hallucinations, hyperkinesia, hypesthesia,
1167 hypokinesia, incoordination, libido increased, neuralgia, neuropathy, nystagmus, paralysis,
1168 vertigo; rare were ataxia, coma, diplopia, dyskinesia, hostility, paranoid reaction, torticollis,
1169 withdrawal syndrome; also observed were abnormal gait, akathisia, akinesia, aphasia,
1170 choreoathetosis, circumoral paresthesia, delirium, delusions, dysarthria, euphoria, extrapyramidal
1171 syndrome, fasciculations, grand mal convulsion, hyperalgesia, irritability, manic reaction,
1172 manic-depressive reaction, meningitis, myelitis, peripheral neuritis, psychosis, psychotic
1173 depression, reflexes decreased, reflexes increased, stupor, trismus.

1174 **Respiratory System:** Frequent were pharyngitis; infrequent were asthma, dyspnea,
1175 epistaxis, laryngitis, pneumonia; rare were stridor; also observed were dysphonia, emphysema,
1176 hemoptysis, hiccups, hyperventilation, lung fibrosis, pulmonary edema, respiratory flu, sputum
1177 increased.

1178 **Skin and Appendages:** Frequent were rash; infrequent were acne, alopecia, dry skin,
1179 eczema, pruritus, urticaria; rare were exfoliative dermatitis, furunculosis, pustular rash,
1180 seborrhea; also observed were angioedema, ecchymosis, erythema multiforme, erythema
1181 nodosum, hirsutism, maculopapular rash, skin discoloration, skin hypertrophy, skin ulcer,
1182 sweating decreased, vesiculobullous rash.

1183 **Special Senses:** Infrequent were conjunctivitis, earache, keratoconjunctivitis, mydriasis,
1184 photophobia, retinal hemorrhage, tinnitus; rare were blepharitis, visual field defect; also observed
1185 were amblyopia, anisocoria, blurred vision, cataract, conjunctival edema, corneal ulcer, deafness,
1186 exophthalmos, glaucoma, hyperacusis, night blindness, parosmia, ptosis, taste loss.

1187 **Urogenital System:** Frequent were dysmenorrhea^{*}; infrequent were albuminuria,
1188 amenorrhea^{*}, breast pain^{*}, cystitis, dysuria, prostatitis^{*}, urinary retention; rare were breast
1189 enlargement^{*}, breast neoplasm^{*}, female lactation, hematuria, kidney calculus, metrorrhagia^{*},
1190 nephritis, nocturia, pregnancy and puerperal disorders^{*}, salpingitis, urinary incontinence, uterine
1191 fibroids enlarged^{*}; also observed were breast atrophy, ejaculatory disturbance, endometrial
1192 disorder, epididymitis, fibrocystic breast, leukorrhea, mastitis, oliguria, polyuria, pyuria,
1193 urethritis, urinary casts, urinary urgency, urolith, uterine spasm, vaginal hemorrhage.

1194 ^{*}Based on the number of men and women as appropriate.

1195 **Postmarketing Reports:** Voluntary reports of adverse events in patients taking
1196 immediate-release paroxetine hydrochloride that have been received since market introduction
1197 and not listed above that may have no causal relationship with the drug include acute
1198 pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis,
1199 and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré
1200 syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, priapism, syndrome of
1201 inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea;
1202 extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity,
1203 dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of

1204 pimozide; tremor and trismus; status epilepticus, acute renal failure, pulmonary hypertension,
1205 allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, restless legs
1206 syndrome (RLS), ventricular fibrillation, ventricular tachycardia (including torsade de pointes),
1207 thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including
1208 aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), vasculitic syndromes
1209 (such as Henoch-Schönlein purpura) and premature births in pregnant women. There has been a
1210 case report of an elevated phenytoin level after 4 weeks of immediate-release paroxetine and
1211 phenytoin coadministration. There has been a case report of severe hypotension when
1212 immediate-release paroxetine was added to chronic metoprolol treatment.

1213 **DRUG ABUSE AND DEPENDENCE**

1214 **Controlled Substance Class:** PAXIL CR is not a controlled substance.

1215 **Physical and Psychologic Dependence:** PAXIL CR has not been systematically studied
1216 in animals or humans for its potential for abuse, tolerance or physical dependence. While the
1217 clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were
1218 not systematic and it is not possible to predict on the basis of this limited experience the extent to
1219 which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently,
1220 patients should be evaluated carefully for history of drug abuse, and such patients should be
1221 observed closely for signs of misuse or abuse of PAXIL CR (e.g., development of tolerance,
1222 incrementations of dose, drug-seeking behavior).

1223 **OVERDOSAGE**

1224 **Human Experience:** Since the introduction of immediate-release paroxetine hydrochloride in
1225 the United States, 342 spontaneous cases of deliberate or accidental overdose during
1226 paroxetine treatment have been reported worldwide (circa 1999). These include overdoses with
1227 paroxetine alone and in combination with other substances. Of these, 48 cases were fatal and of
1228 the fatalities, 17 appeared to involve paroxetine alone. Eight fatal cases that documented the
1229 amount of paroxetine ingested were generally confounded by the ingestion of other drugs or
1230 alcohol or the presence of significant comorbid conditions. Of 145 non-fatal cases with known
1231 outcome, most recovered without sequelae. The largest known ingestion involved 2,000 mg of
1232 paroxetine (33 times the maximum recommended daily dose) in a patient who recovered.

1233 Commonly reported adverse events associated with paroxetine overdose include
1234 somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other
1235 notable signs and symptoms observed with overdoses involving paroxetine (alone or with other
1236 substances) include mydriasis, convulsions (including status epilepticus), ventricular
1237 dysrhythmias (including torsade de pointes), hypertension, aggressive reactions, syncope,
1238 hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction
1239 (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin
1240 syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

1241 **Overdosage Management:** No specific antidotes for paroxetine are known. Treatment
1242 should consist of those general measures employed in the management of overdose with any

1243 drugs effective in the treatment of major depressive disorder.

1244 Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital
1245 signs. General supportive and symptomatic measures are also recommended. Induction of emesis
1246 is not recommended. Due to the large volume of distribution of this drug, forced diuresis,
1247 dialysis, hemoperfusion, or exchange perfusion are unlikely to be of benefit.

1248 A specific caution involves patients taking or recently having taken paroxetine who might
1249 ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the
1250 parent tricyclic and an active metabolite may increase the possibility of clinically significant
1251 sequelae and extend the time needed for close medical observation (see PRECAUTIONS: *Drugs*
1252 *Metabolized by Cytochrome CYP2D6*).

1253 In managing overdose, consider the possibility of multiple-drug involvement. The physician
1254 should consider contacting a poison control center for additional information on the treatment of
1255 any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians'*
1256 *Desk Reference* (PDR).

1257 **DOSAGE AND ADMINISTRATION**

1258 **Major Depressive Disorder: Usual Initial Dosage:** PAXIL CR should be administered as
1259 a single daily dose, usually in the morning, with or without food. The recommended initial dose
1260 is 25 mg/day. Patients were dosed in a range of 25 mg to 62.5 mg/day in the clinical trials
1261 demonstrating the effectiveness of PAXIL CR in the treatment of major depressive disorder. As
1262 with all drugs effective in the treatment of major depressive disorder, the full effect may be
1263 delayed. Some patients not responding to a 25-mg dose may benefit from dose increases, in
1264 12.5-mg/day increments, up to a maximum of 62.5 mg/day. Dose changes should occur at
1265 intervals of at least 1 week.

1266 Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be
1267 swallowed whole.

1268 **Maintenance Therapy:** There is no body of evidence available to answer the question of
1269 how long the patient treated with PAXIL CR should remain on it. It is generally agreed that acute
1270 episodes of major depressive disorder require several months or longer of sustained
1271 pharmacologic therapy. Whether the dose of an antidepressant needed to induce remission is
1272 identical to the dose needed to maintain and/or sustain euthymia is unknown.

1273 Systematic evaluation of the efficacy of immediate-release paroxetine hydrochloride has
1274 shown that efficacy is maintained for periods of up to 1 year with doses that averaged about
1275 30 mg, which corresponds to a 37.5-mg dose of PAXIL CR, based on relative bioavailability
1276 considerations (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

1277

1278 **Panic Disorder: Usual Initial Dosage:** PAXIL CR should be administered as a single daily
1279 dose, usually in the morning. Patients should be started on 12.5 mg/day. Dose changes should
1280 occur in 12.5-mg/day increments and at intervals of at least 1 week. Patients were dosed in a
1281 range of 12.5 to 75 mg/day in the clinical trials demonstrating the effectiveness of PAXIL CR.
1282 The maximum dosage should not exceed 75 mg/day.

1283 Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be
1284 swallowed whole.

1285 **Maintenance Therapy:** Long-term maintenance of efficacy with the immediate-release
1286 formulation of paroxetine was demonstrated in a 3-month relapse prevention trial. In this trial,
1287 patients with panic disorder assigned to immediate-release paroxetine demonstrated a lower
1288 relapse rate compared to patients on placebo. Panic disorder is a chronic condition, and it is
1289 reasonable to consider continuation for a responding patient. Dosage adjustments should be
1290 made to maintain the patient on the lowest effective dosage, and patients should be periodically
1291 reassessed to determine the need for continued treatment.

1292 **Social Anxiety Disorder: Usual Initial Dosage:** PAXIL CR should be administered as a
1293 single daily dose, usually in the morning, with or without food. The recommended initial dose is
1294 12.5 mg/day. Patients were dosed in a range of 12.5 mg to 37.5 mg/day in the clinical trial
1295 demonstrating the effectiveness of PAXIL CR in the treatment of social anxiety disorder. If the
1296 dose is increased, this should occur at intervals of at least 1 week, in increments of 12.5 mg/day,
1297 up to a maximum of 37.5 mg/day.

1298 Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be
1299 swallowed whole.

1300 **Maintenance Therapy:** There is no body of evidence available to answer the question of
1301 how long the patient treated with PAXIL CR should remain on it. Although the efficacy of
1302 PAXIL CR beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials,
1303 social anxiety disorder is recognized as a chronic condition, and it is reasonable to consider
1304 continuation of treatment for a responding patient. Dosage adjustments should be made to
1305 maintain the patient on the lowest effective dosage, and patients should be periodically
1306 reassessed to determine the need for continued treatment.

1307 **Premenstrual Dysphoric Disorder: Usual Initial Dosage:** PAXIL CR should be
1308 administered as a single daily dose, usually in the morning, with or without food. PAXIL CR
1309 may be administered either daily throughout the menstrual cycle or limited to the luteal phase of
1310 the menstrual cycle, depending on physician assessment. The recommended initial dose is
1311 12.5 mg/day. In clinical trials, both 12.5 mg/day and 25 mg/day were shown to be effective.
1312 Dose changes should occur at intervals of at least 1 week.

1313 Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be
1314 swallowed whole.

1315 **Maintenance/Continuation Therapy:** The effectiveness of PAXIL CR for a period
1316 exceeding 3 menstrual cycles has not been systematically evaluated in controlled trials.
1317 However, women commonly report that symptoms worsen with age until relieved by the onset of

1318 menopause. Therefore, it is reasonable to consider continuation of a responding patient. Patients
1319 should be periodically reassessed to determine the need for continued treatment.

1320 **Special Populations: Treatment of Pregnant Women During the Third Trimester:**

1321 Neonates exposed to PAXIL CR and other SSRIs or SNRIs, late in the third trimester have
1322 developed complications requiring prolonged hospitalization, respiratory support, and tube
1323 feeding (see WARNINGS: Usage in Pregnancy). When treating pregnant women with paroxetine
1324 during the third trimester, the physician should carefully consider the potential risks and benefits
1325 of treatment.

1326 **Dosage for Elderly or Debilitated Patients, and Patients With Severe Renal or**
1327 **Hepatic Impairment:** The recommended initial dose of PAXIL CR is 12.5 mg/day for elderly
1328 patients, debilitated patients, and/or patients with severe renal or hepatic impairment. Increases
1329 may be made if indicated. Dosage should not exceed 50 mg/day.

1330 **Switching a Patient to or From a Monoamine Oxidase Inhibitor (MAOI) Intended to**

1331 **Treat Psychiatric Disorders:** At least 14 days should elapse between discontinuation of an
1332 MAOI intended to treat psychiatric disorders and initiation of therapy with PAXIL CR.

1333 Conversely, at least 14 days should be allowed after stopping PAXIL CR before starting an
1334 MAOI intended to treat psychiatric disorders (see CONTRAINDICATIONS).

1335 **Use of PAXIL CR With Other MAOIs, Such as Linezolid or Methylene Blue:** Do not
1336 start PAXIL CR in a patient who is being treated with linezolid or intravenous methylene blue
1337 because there is increased risk of serotonin syndrome. In a patient who requires more urgent
1338 treatment of a psychiatric condition, other interventions, including hospitalization, should be
1339 considered (see CONTRAINDICATIONS).

1340 In some cases, a patient already receiving therapy with PAXIL CR may require urgent
1341 treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or
1342 intravenous methylene blue treatment are not available and the potential benefits of linezolid or
1343 intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in
1344 a particular patient, PAXIL CR should be stopped promptly, and linezolid or intravenous
1345 methylene blue can be administered. The patient should be monitored for symptoms of serotonin
1346 syndrome for 2 weeks or until 24 hours after the last dose of linezolid or intravenous methylene
1347 blue, whichever comes first. Therapy with PAXIL CR may be resumed 24 hours after the last
1348 dose of linezolid or intravenous methylene blue (see WARNINGS).

1349 The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by
1350 local injection) or in intravenous doses much lower than 1 mg/kg with PAXIL CR is unclear.
1351 The clinician should, nevertheless, be aware of the possibility of emergent symptoms of
1352 serotonin syndrome with such use (see WARNINGS).

1353 **Discontinuation of Treatment With PAXIL CR:** Symptoms associated with discontinuation
1354 of immediate-release paroxetine hydrochloride or PAXIL CR have been reported (see
1355 PRECAUTIONS: *Discontinuation of Treatment with PAXIL CR*). Patients should be monitored
1356 for these symptoms when discontinuing treatment, regardless of the indication for which PAXIL
1357 CR is being prescribed. A gradual reduction in the dose rather than abrupt cessation is

1358 recommended whenever possible. If intolerable symptoms occur following a decrease in the dose
1359 or upon discontinuation of treatment, then resuming the previously prescribed dose may be
1360 considered. Subsequently, the physician may continue decreasing the dose but at a more gradual
1361 rate.

1362 **HOW SUPPLIED**

1363 PAXIL CR is supplied as an enteric film-coated, controlled-release, round tablet, as follows:

1364 12.5-mg yellow tablets

1365 NDC 0029-3206-13 Bottles of 30 (engraved with PAXIL CR and 12.5)

1366 NDC 0029-4606-13 Bottles of 30 (engraved with GSK and 12.5)

1367 25-mg pink tablets

1368 NDC 0029-3207-13 Bottles of 30 (engraved with PAXIL CR and 25)

1369 NDC 0029-4607-13 Bottles of 30 (engraved with GSK and 25)

1370 37.5 mg blue tablets

1371 NDC 0029-3208-13 Bottles of 30 (engraved with PAXIL CR and 37.5)

1372 NDC 0029-4608-13 Bottles of 30 (engraved with GSK and 37.5)

1373 Store at or below 25°C (77°F) [see USP].

1374

1375 PAXIL CR is a registered trademark of GlaxoSmithKline.

1376 GEOMATRIX is a trademark of Jago Pharma, Muttenz, Switzerland.



GlaxoSmithKline

1377

1378

GlaxoSmithKline

Research Triangle Park, NC 27709

1379 ©Year, GlaxoSmithKline. All rights reserved.

1380

1381 **Month Year**

PCR:XXPI

1382

1383

1384
1385
1386
1387
1388
1389
1390
1391
1392
1393
1394
1395
1396
1397
1398
1399
1400
1401
1402
1403
1404
1405
1406
1407
1408
1409
1410
1411
1412
1413
1414
1415
1416
1417
1418
1419
1420
1421
1422
1423

Medication Guide
PAXIL CR® (PAX-il) (paroxetine hydrochloride)
Controlled-Release Tablets

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

What is the most important information I should know about PAXIL CR?

PAXIL CR and other antidepressant medicines may cause serious side effects, including:

1. Suicidal thoughts or actions:

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

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

Call your healthcare provider right away if you have any of the following symptoms, or call 911 if an emergency, especially if they are new, worse, or worry you:

- attempts to commit suicide
- acting on dangerous impulses
- acting aggressive or violent
- thoughts about suicide or dying
- new or worse depression
- new or worse anxiety or panic attacks
- feeling agitated, restless, angry, or irritable
- trouble sleeping
- an increase in activity and talking more than what is normal for you
- other unusual changes in behavior or mood

Call your healthcare provider right away if you have any of the following symptoms, or call

- 1424 **911 if an emergency. PAXIL CR may be associated with these serious side effects:**
- 1425 **2. Serotonin Syndrome or Neuroleptic Malignant Syndrome-like reactions. This**
- 1426 **condition can be life-threatening and may include:**
- 1427 • agitation, hallucinations, coma, or other changes in mental status
- 1428 • coordination problems or muscle twitching (overactive reflexes)
- 1429 • racing heartbeat, high or low blood pressure
- 1430 • sweating or fever
- 1431 • nausea, vomiting, or diarrhea
- 1432 • muscle rigidity
- 1433 **3. Severe allergic reactions:**
- 1434 • trouble breathing
- 1435 • swelling of the face, tongue, eyes, or mouth
- 1436 • rash, itchy welts (hives), or blisters, alone or with fever or joint pain
- 1437 **4. Abnormal bleeding:** PAXIL CR and other antidepressant medicines may increase your
- 1438 risk of bleeding or bruising, especially if you take the blood thinner warfarin (Coumadin[®],
- 1439 Jantoven[®]), a non-steroidal anti-inflammatory drug (NSAIDs, like ibuprofen or naproxen),
- 1440 or aspirin.
- 1441 **5. Seizures or convulsions**
- 1442 **6. Manic episodes:**
- 1443 • greatly increased energy
- 1444 • severe trouble sleeping
- 1445 • racing thoughts
- 1446 • reckless behavior
- 1447 • unusually grand ideas
- 1448 • excessive happiness or irritability
- 1449 • talking more or faster than usual
- 1450 **7. Changes in appetite or weight.**
- 1451 Children and adolescents should have height and weight monitored during treatment.
- 1452 **8. Low salt (sodium) levels in the blood.**
- 1453 Elderly people may be at greater risk for this. Symptoms may include:
- 1454 • headache
- 1455 • weakness or feeling unsteady
- 1456 • confusion, problems concentrating or thinking, or memory problems
- 1457
- 1458 **Do not stop PAXIL CR without first talking to your healthcare provider.** Stopping PAXIL
- 1459 CR too quickly may cause serious symptoms including:
- 1460 • anxiety, irritability, high or low mood, feeling restless, or changes in sleep habits
- 1461 • headache, sweating, nausea, dizziness
- 1462 • electric shock-like sensations, shaking, confusion
- 1463

1464 **What is PAXIL CR?**

1465 PAXIL CR is a prescription medicine used to treat depression. It is important to talk with your
1466 healthcare provider about the risks of treating depression and also the risks of not treating it. You
1467 should discuss all treatment choices with your healthcare provider. PAXIL CR is also used to
1468 treat:

- 1469 • Major Depressive Disorder (MDD)
- 1470 • Panic Disorder
- 1471 • Social Anxiety Disorder
- 1472 • Premenstrual Dysphoric Disorder (PMDD)

1473 Talk to your healthcare provider if you do not think that your condition is getting better with
1474 treatment using PAXIL CR.

1475

1476 **Who should not take PAXIL CR?**

1477 Do not take PAXIL CR if you:

- 1478 • are allergic to paroxetine or any of the ingredients in PAXIL CR. See the end of this
1479 Medication Guide for a complete list of ingredients in PAXIL CR.
- 1480 • take a monoamine oxidase inhibitor (MAOI). Ask your healthcare provider or pharmacist if
1481 you are not sure if you take an MAOI, including the antibiotic linezolid.
 - 1482 • Do not take an MAOI within 2 weeks of stopping PAXIL CR unless directed to do so by
1483 your physician.
 - 1484 • Do not start PAXIL CR if you stopped taking an MAOI in the last 2 weeks unless
1485 directed to do so by your physician.
 - 1486 • **People who take PAXIL CR close in time to an MAOI may have serious or even life-**
1487 **threatening side effects. Get medical help right away if you have any of these**
1488 **symptoms:**
 - 1489 • high fever
 - 1490 • uncontrolled muscle spasms
 - 1491 • stiff muscles
 - 1492 • rapid changes in heart rate or blood pressure
 - 1493 • confusion
 - 1494 • loss of consciousness (pass out)
 - 1495 • **take MELLARIL[®] (thioridazine). Do not take MELLARIL[®] together with PAXIL CR**
1496 **because this can cause serious heart rhythm problems or sudden death.**
 - 1497 • **take the antipsychotic medicine pimozide (ORAP[®]) because this can cause serious heart**
1498 **problems.**

1499

1500 **What should I tell my healthcare provider before taking PAXIL CR? Ask if you are not**
1501 **sure.**

1502 Before starting PAXIL CR, tell your healthcare provider if you:

- 1503 • **are pregnant, may be pregnant, or plan to become pregnant.** There is a possibility that
1504 PAXIL CR may harm your unborn baby, including an increased risk of birth defects,
1505 particularly heart defects. Other risks may include a serious condition in which there is not
1506 enough oxygen in the baby’s blood. Your baby may also have certain other symptoms shortly
1507 after birth. Premature births have also been reported in some women who used PAXIL CR
1508 during pregnancy.
- 1509 • **are breastfeeding.** PAXIL CR passes into your milk. Talk to your healthcare provider about
1510 the best way to feed your baby while taking PAXIL CR.
- 1511 • are taking certain drugs such as:
- 1512 • triptans used to treat migraine headache
 - 1513 • other antidepressants (SSRIs, SNRIs, tricyclics, or lithium) or antipsychotics
 - 1514 • drugs that affect serotonin, such as lithium, tramadol, tryptophan, St. John’s wort
 - 1515 • certain drugs used to treat irregular heart beats
 - 1516 • certain drugs used to treat schizophrenia
 - 1517 • certain drugs used to treat HIV infection
 - 1518 • certain drugs that affect the blood, such as warfarin, aspirin, and ibuprofen
 - 1519 • certain drugs used to treat epilepsy
 - 1520 • atomoxetine
 - 1521 • cimetidine
 - 1522 • fentanyl
 - 1523 • metoprolol
 - 1524 • pimozone
 - 1525 • procyclidine
 - 1526 • tamoxifen
- 1527 • have liver problems
- 1528 • have kidney problems
- 1529 • have heart problems
- 1530 • have or had seizures or convulsions
- 1531 • have bipolar disorder or mania
- 1532 • have low sodium levels in your blood
- 1533 • have a history of a stroke
- 1534 • have high blood pressure
- 1535 • have or had bleeding problems
- 1536 • have glaucoma (high pressure in the eye)
- 1537
- 1538 **Tell your healthcare provider about all the medicines you take,** including prescription and
1539 non-prescription medicines, vitamins, and herbal supplements. PAXIL CR and some medicines
1540 may interact with each other, may not work as well, or may cause serious side effects.

1541 Your healthcare provider or pharmacist can tell you if it is safe to take PAXIL CR with your
1542 other medicines. Do not start or stop any medicine while taking PAXIL CR without talking to
1543 your healthcare provider first.

1544 If you take PAXIL CR, you should not take any other medicines that contain paroxetine,
1545 including PAXIL and PEXEVA[®] (paroxetine mesylate).

1546

1547 **How should I take PAXIL CR?**

- 1548 • Take PAXIL CR exactly as prescribed. Your healthcare provider may need to change the
1549 dose of PAXIL CR until it is the right dose for you.
- 1550 • PAXIL CR may be taken with or without food.
- 1551 • PAXIL CR controlled-release tablets should not be chewed or crushed and should be
1552 swallowed whole.
- 1553 • If you miss a dose of PAXIL CR, take the missed dose as soon as you remember. If it is
1554 almost time for the next dose, skip the missed dose and take your next dose at the regular
1555 time. Do not take two doses of PAXIL CR at the same time.
- 1556 • If you take too much PAXIL CR, call your healthcare provider or poison control center right
1557 away, or get emergency treatment.
- 1558 • Do not stop taking PAXIL CR suddenly without talking to your doctor (unless you have
1559 symptoms of a severe allergic reaction). If you need to stop taking PAXIL CR, your
1560 healthcare provider can tell you how to safely stop taking it.

1561

1562 **What should I avoid while taking PAXIL CR?**

1563 PAXIL CR can cause sleepiness or may affect your ability to make decisions, think clearly, or
1564 react quickly. You should not drive, operate heavy machinery, or do other dangerous activities
1565 until you know how PAXIL CR affects you. Do not drink alcohol while using PAXIL CR.

1566

1567 **What are possible side effects of PAXIL CR?**

1568 PAXIL CR may cause serious side effects, including all of those described in the section entitled
1569 “What is the most important information I should know about PAXIL CR?”

1570 Common possible side effects in people who take PAXIL CR include:

- 1571 • nausea
- 1572 • sleepiness
- 1573 • feeling anxious or trouble sleeping
- 1574 • sexual problems
- 1575 • sweating
- 1576 • shaking
- 1577 • constipation
- 1578 • yawning

- 1579 • blurred vision
- 1580 • diarrhea
- 1581 • dry mouth
- 1582 • decreased appetite
- 1583 • weakness

1584

1585 Tell your healthcare provider if you have any side effect that bothers you or that does not go
1586 away. These are not all the possible side effects of PAXIL CR. For more information, ask your
1587 healthcare provider or pharmacist.

1588

1589 **CALL YOUR DOCTOR FOR MEDICAL ADVICE ABOUT SIDE EFFECTS. YOU MAY**
1590 **REPORT SIDE EFFECTS TO THE FDA AT 1-800-FDA-1088 or 1-800-332-1088.**

1591

1592 **How should I store PAXIL CR?**

- 1593 • Store PAXIL CR at or below room temperature (77°F or 25°C).
- 1594 • Keep PAXIL CR away from light.
- 1595 • Keep bottle of PAXIL CR closed tightly.

1596 **Keep PAXIL CR and all medicines out of the reach of children.**

1597

1598 **General information about PAXIL CR**

1599 Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.
1600 Do not use PAXIL CR for a condition for which it was not prescribed. Do not give PAXIL CR to
1601 other people, even if they have the same condition. It may harm them.

1602

1603 This Medication Guide summarizes the most important information about PAXIL CR. If you
1604 would like more information, talk with your healthcare provider. You may ask your healthcare
1605 provider or pharmacist for information about PAXIL CR that is written for healthcare
1606 professionals.

1607

1608 For more information about PAXIL CR call 1-888-825-5249 or go to www.us.gsk.com.

1609

1610 **What are the ingredients in PAXIL CR?**

1611 **Active ingredient:** paroxetine hydrochloride

1612 **Inactive ingredients in tablets:** hypromellose, polyvinylpyrrolidone, lactose monohydrate,
1613 magnesium stearate, silicon dioxide, glyceryl behenate, methacrylic acid copolymer type C,
1614 sodium lauryl sulfate, polysorbate 80, talc, triethyl citrate, titanium dioxide, polyethylene
1615 glycols, and 1 or more of the following colorants: Yellow ferric oxide, red ferric oxide, D&C
1616 Red No. 30 aluminum lake, FD&C Yellow No. 6 aluminum lake, D&C Yellow No. 10
1617 aluminum lake, FD&C Blue No. 2 aluminum lake.

1618
1619 PAXIL and PAXIL CR are registered trademarks of GlaxoSmithKline. The other brands listed
1620 are trademarks of their respective owners and are not trademarks of GlaxoSmithKline. The
1621 makers of these brands are not affiliated with and do not endorse GlaxoSmithKline or its
1622 products.

1623
1624 This Medication Guide has been approved by the U.S. Food and Drug Administration.

1625
1626

1627  GlaxoSmithKline

GlaxoSmithKline
Research Triangle Park, NC 27709

1628 ©2011, GlaxoSmithKline. All rights reserved.

1629

1630 December 2012

PCR:XX

1631