

PRESCRIBING INFORMATION

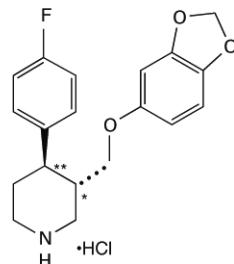
PAXIL CR[®]
(paroxetine hydrochloride)
Controlled-Release Tablets

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-HT₁-, 5-HT₂-, 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 **Absorption and Distribution:** Tablets of PAXIL CR contain a degradable polymeric
58 matrix (GEOMATRIX™) designed to control the dissolution rate of paroxetine over a period of
59 approximately 4 to 5 hours. In addition to controlling the rate of drug release in vivo, an enteric
60 coat delays the start of drug release until tablets of PAXIL CR have left the stomach.

61 Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the
62 hydrochloride salt. In a study in which normal male and female subjects (n = 23) received single
63 oral doses of PAXIL CR at 4 dosage strengths (12.5 mg, 25 mg, 37.5 mg, and 50 mg), paroxetine
64 C_{max} and AUC_{0-inf} increased disproportionately with dose (as seen also with immediate-release
65 formulations). Mean C_{max} and AUC_{0-inf} values at these doses were 2.0, 5.5, 9.0, and 12.5 ng/mL,
66 and 121, 261, 338, and 540 ng•hr./mL, respectively. T_{max} was observed typically between 6 and
67 10 hours post-dose, reflecting a reduction in absorption rate compared with immediate-release
68 formulations. The bioavailability of 25 mg PAXIL CR is not affected by food.

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

71 Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/mL and
72 400 ng/mL, respectively. Under clinical conditions, paroxetine concentrations would normally be

73 less than 400 ng/mL. Paroxetine does not alter the in vitro protein binding of phenytoin or
74 warfarin.

75 **Metabolism and Excretion:** The mean elimination half-life of paroxetine was 15 to
76 20 hours throughout a range of single doses of PAXIL CR (12.5 mg, 25 mg, 37.5 mg, and
77 50 mg). During repeated administration of PAXIL CR (25 mg once daily), steady state was
78 reached within 2 weeks (i.e., comparable to immediate-release formulations). In a repeat-dose
79 study in which normal male and female subjects (n = 23) received PAXIL CR (25 mg daily),
80 mean steady state C_{max} , C_{min} , and AUC_{0-24} values were 30 ng/mL, 20 ng/mL, and 550 ng•hr./mL,
81 respectively.

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

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

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

100 Approximately 64% of a 30-mg oral solution dose of paroxetine was excreted in the urine
101 with 2% as the parent compound and 62% as metabolites over a 10-day post-dosing period.
102 About 36% was excreted in the feces (probably via the bile), mostly as metabolites and less than
103 1% as the parent compound over the 10-day post-dosing period.

104 **Other Clinical Pharmacology Information: Specific Populations: Renal and Liver**
105 **Disease:** Increased plasma concentrations of paroxetine occur in subjects with renal and hepatic
106 impairment. The mean plasma concentrations in patients with creatinine clearance below
107 30 mL/min. were approximately 4 times greater than seen in normal volunteers. Patients with
108 creatinine clearance of 30 to 60 mL/min. and patients with hepatic functional impairment had
109 about a 2-fold increase in plasma concentrations (AUC , C_{max}).

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

113 **Elderly Patients:** In a multiple-dose study in the elderly at daily doses of 20, 30, and
114 40 mg of the immediate-release formulation, C_{min} concentrations were about 70% to 80% greater
115 than the respective C_{min} concentrations in nonelderly subjects. Therefore the initial dosage in the
116 elderly should be reduced (see DOSAGE AND ADMINISTRATION).

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

121 **Clinical Trials**

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

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

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

146 For all 3 studies, the mean dose of PAXIL CR for completers at endpoint was approximately
147 50 mg/day. Subgroup analyses did not indicate that there were any differences in treatment
148 outcomes as a function of age or gender.

149 Long-term maintenance effects of the immediate-release formulation of paroxetine in panic
150 disorder were demonstrated in an extension study. Patients who were responders during a
151 10-week double-blind phase with immediate-release paroxetine and during a 3-month

152 double-blind extension phase were randomized to either immediate-release paroxetine or placebo
153 in a 3-month double-blind relapse prevention phase. Patients randomized to paroxetine were
154 significantly less likely to relapse than comparably treated patients who were randomized to
155 placebo.

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

166 PAXIL CR demonstrated statistically significant superiority over placebo on both the LSAS
167 total score and the CGI Improvement responder criterion. For patients who completed the trial,
168 64% of patients treated with PAXIL CR compared to 34.7% of patients treated with placebo
169 were CGI Improvement responders.

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

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

188 In a third study employing intermittent dosing, patients (N = 366) were treated for the 2 weeks
189 prior to the onset of menses (luteal phase dosing, also known as intermittent dosing) with
190 12.5 mg/day or 25 mg/day of PAXIL CR or placebo for a period of 3 months. 12.5 mg/day and
191 25 mg/day of PAXIL CR, as luteal phase dosing, was significantly more effective than placebo

192 as measured by change from baseline luteal phase VAS total score.

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

195 **INDICATIONS AND USAGE**

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

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

201 A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly
202 every day for at least 2 weeks) depressed mood or loss of interest or pleasure in nearly all
203 activities, representing a change from previous functioning, and includes the presence of at least
204 5 of the following 9 symptoms during the same 2-week period: Depressed mood, markedly
205 diminished interest or pleasure in usual activities, significant change in weight and/or appetite,
206 insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of
207 guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt, or suicidal
208 ideation.

209 The antidepressant action of paroxetine in hospitalized depressed patients has not been
210 adequately studied.

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

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

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

225 Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, i.e., a
226 discrete period of intense fear or discomfort in which 4 (or more) of the following symptoms
227 develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or
228 accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of
229 breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or
230 abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings

231 of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11)
232 fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

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

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

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

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

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

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

263 The essential features of PMDD, according to DSM-IV, include markedly depressed mood,
264 anxiety or tension, affective lability, and persistent anger or irritability. Other features include
265 decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite
266 or sleep, and feeling out of control. Physical symptoms associated with PMDD include breast
267 tenderness, headache, joint and muscle pain, bloating, and weight gain. These symptoms occur
268 regularly during the luteal phase and remit within a few days following the onset of menses; the
269 disturbance markedly interferes with work or school or with usual social activities and
270 relationships with others. In making the diagnosis, care should be taken to rule out other cyclical

271 mood disorders that may be exacerbated by treatment with an antidepressant.

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

276 **CONTRAINDICATIONS**

277 Concomitant use in patients taking either monoamine oxidase inhibitors (MAOIs), including
278 linezolid, an antibiotic which is a reversible non-selective MAOI, or thioridazine is
279 contraindicated (see WARNINGS and PRECAUTIONS).

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

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

283 **WARNINGS**

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

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

309 **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

310

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

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

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

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

327 Consideration should be given to changing the therapeutic regimen, including possibly
328 discontinuing the medication, in patients whose depression is persistently worse, or who are
329 experiencing emergent suicidality or symptoms that might be precursors to worsening depression
330 or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the
331 patient's presenting symptoms.

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

337 **Families and caregivers of patients being treated with antidepressants for major**
338 **depressive disorder or other indications, both psychiatric and nonpsychiatric, should be**
339 **alerted about the need to monitor patients for the emergence of agitation, irritability,**
340 **unusual changes in behavior, and the other symptoms described above, as well as the**

341 **emergence of suicidality, and to report such symptoms immediately to healthcare**
342 **providers. Such monitoring should include daily observation by families and caregivers.**
343 Prescriptions for PAXIL CR should be written for the smallest quantity of tablets consistent with
344 good patient management, in order to reduce the risk of overdose.

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

355 **Potential for Interaction With Monoamine Oxidase Inhibitors:** In patients receiving
356 another serotonin reuptake inhibitor drug in combination with an MAOI, there have been
357 reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus,
358 autonomic instability with possible rapid fluctuations of vital signs, and mental status
359 changes that include extreme agitation progressing to delirium and coma. These reactions
360 have also been reported in patients who have recently discontinued that drug and have
361 been started on an MAOI. Some cases presented with features resembling neuroleptic
362 malignant syndrome. While there are no human data showing such an interaction with
363 paroxetine hydrochloride, limited animal data on the effects of combined use of paroxetine
364 and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and
365 evoke behavioral excitation. Therefore, it is recommended that PAXIL CR not be used in
366 combination with an MAOI (including linezolid, an antibiotic which is a reversible non-
367 selective MAOI), or within 14 days of discontinuing treatment with an MAOI (see
368 **CONTRAINDICATIONS**). At least 2 weeks should be allowed after stopping PAXIL CR
369 before starting an MAOI.

370 **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions:**
371 **The development of a potentially life-threatening serotonin syndrome or Neuroleptic**
372 **Malignant Syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs**
373 **alone, including treatment with PAXIL CR, but particularly with concomitant use of**
374 **serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin**
375 **(including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin**
376 **syndrome symptoms may include mental status changes (e.g., agitation, hallucinations,**
377 **coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia),**
378 **neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal**
379 **symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form**
380 **can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle**

381 **rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental**
382 **status changes. Patients should be monitored for the emergence of serotonin syndrome or**
383 **NMS-like signs and symptoms.**

384 **The concomitant use of PAXIL CR with MAOIs intended to treat depression is**
385 **contraindicated.**

386 **If concomitant treatment of PAXIL CR with a 5-hydroxytryptamine receptor agonist**
387 **(triptan) is clinically warranted, careful observation of the patient is advised, particularly**
388 **during treatment initiation and dose increases.**

389 **The concomitant use of PAXIL CR with serotonin precursors (such as tryptophan) is**
390 **not recommended.**

391 **Treatment with PAXIL CR and any concomitant serotonergic or antidopaminergic**
392 **agents, including antipsychotics, should be discontinued immediately if the above events**
393 **occur and supportive symptomatic treatment should be initiated.**

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

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

402 **Usage in Pregnancy: *Teratogenic Effects:*** Epidemiological studies have shown that
403 infants born to women who had first trimester paroxetine exposure had an increased risk of
404 cardiovascular malformations, primarily ventricular and atrial septal defects (VSDs and ASDs).
405 In general, septal defects range from those that are symptomatic and may require surgery to those
406 that are asymptomatic and may resolve spontaneously. If a patient becomes pregnant while
407 taking paroxetine, she should be advised of the potential harm to the fetus. Unless the benefits of
408 paroxetine to the mother justify continuing treatment, consideration should be given to either
409 discontinuing paroxetine therapy or switching to another antidepressant (see PRECAUTIONS:
410 Discontinuation of Treatment with PAXIL CR). For women who intend to become pregnant or
411 are in their first trimester of pregnancy, paroxetine should only be initiated after consideration of
412 the other available treatment options.

413 A study based on Swedish national registry data evaluated infants of 6,896 women exposed to
414 antidepressants in early pregnancy (5,123 women exposed to SSRIs; including 815 for
415 paroxetine). Infants exposed to paroxetine in early pregnancy had an increased risk of
416 cardiovascular malformations (primarily VSDs and ASDs) compared to the entire registry
417 population (OR 1.8; 95% confidence interval 1.1-2.8). The rate of cardiovascular malformations
418 following early pregnancy paroxetine exposure was 2% vs. 1% in the entire registry population.
419 Among the same paroxetine exposed infants, an examination of the data showed no increase in
420 the overall risk for congenital malformations.

421 A separate retrospective cohort study using US United Healthcare data evaluated 5,956 infants
422 of mothers dispensed paroxetine or other antidepressants during the first trimester (n = 815 for
423 paroxetine). This study showed a trend towards an increased risk for cardiovascular
424 malformations for paroxetine compared to other antidepressants (OR 1.5; 95% confidence
425 interval 0.8-2.9). The prevalence of cardiovascular malformations following first trimester
426 dispensing was 1.5% for paroxetine vs. 1% for other antidepressants. Nine out of 12 infants with
427 cardiovascular malformations whose mothers were dispensed paroxetine in the first trimester had
428 VSDs. This study also suggested an increased risk of overall major congenital malformations
429 (inclusive of the cardiovascular defects) for paroxetine compared to other antidepressants (OR
430 1.8; 95% confidence interval 1.2-2.8). The prevalence of all congenital malformations following
431 first trimester exposure was 4% for paroxetine vs. 2% for other antidepressants.

432 **Animal Findings:** Reproduction studies were performed at doses up to 50 mg/kg/day in rats
433 and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately
434 8 (rat) and 2 (rabbit) times the maximum recommended human dose (MRHD) on an mg/m²
435 basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was
436 an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last
437 trimester of gestation and continued throughout lactation. This effect occurred at a dose of
438 1 mg/kg/day or approximately one-sixth of the MRHD on an mg/m² basis. The no-effect dose for
439 rat pup mortality was not determined. The cause of these deaths is not known.

440 **Nonteratogenic Effects:** Neonates exposed to PAXIL CR and other SSRIs or serotonin
441 and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed
442 complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such
443 complications can arise immediately upon delivery. Reported clinical findings have included
444 respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty,
445 vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and
446 constant crying. These features are consistent with either a direct toxic effect of SSRIs and
447 SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the
448 clinical picture is consistent with serotonin syndrome (see WARNINGS: Serotonin Syndrome or
449 Neuroleptic Malignant Syndrome (NMS)-like Reactions).

450 Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent
451 pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 – 2 per 1,000 live births in
452 the general population and is associated with substantial neonatal morbidity and mortality. In a
453 retrospective case-control study of 377 women whose infants were born with PPHN and 836
454 women whose infants were born healthy, the risk for developing PPHN was approximately six-
455 fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who
456 had not been exposed to antidepressants during pregnancy. There is currently no corroborative
457 evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first
458 study that has investigated the potential risk. The study did not include enough cases with
459 exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk.

460 There have also been postmarketing reports of premature births in pregnant women exposed

461 to paroxetine or other SSRIs.

462 When treating a pregnant woman with paroxetine during the third trimester, the physician
463 should carefully consider both the potential risks and benefits of treatment (see DOSAGE AND
464 ADMINISTRATION). Physicians should note that in a prospective longitudinal study of 201
465 women with a history of major depression who were euthymic at the beginning of pregnancy,
466 women who discontinued antidepressant medication during pregnancy were more likely to
467 experience a relapse of major depression than women who continued antidepressant medication.

468 **PRECAUTIONS**

469 **General: Activation of Mania/Hypomania:** During premarketing testing of
470 immediate-release paroxetine hydrochloride, hypomania or mania occurred in approximately
471 1.0% of paroxetine-treated unipolar patients compared to 1.1% of active-control and 0.3% of
472 placebo-treated unipolar patients. In a subset of patients classified as bipolar, the rate of manic
473 episodes was 2.2% for immediate-release paroxetine and 11.6% for the combined active-control
474 groups. Among 1,627 patients with major depressive disorder, panic disorder, social anxiety
475 disorder, or PMDD treated with PAXIL CR in controlled clinical studies, there were no reports
476 of mania or hypomania. As with all drugs effective in the treatment of major depressive disorder,
477 PAXIL CR should be used cautiously in patients with a history of mania.

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

485 **Discontinuation of Treatment With PAXIL CR:** Adverse events while discontinuing
486 therapy with PAXIL CR were not systematically evaluated in most clinical trials; however, in
487 recent placebo-controlled clinical trials utilizing daily doses of PAXIL CR up to 37.5 mg/day,
488 spontaneously reported adverse events while discontinuing therapy with PAXIL CR were
489 evaluated. Patients receiving 37.5 mg/day underwent an incremental decrease in the daily dose
490 by 12.5 mg/day to a dose of 25 mg/day for 1 week before treatment was stopped. For patients
491 receiving 25 mg/day or 12.5 mg/day, treatment was stopped without an incremental decrease in
492 dose. With this regimen in those studies, the following adverse events were reported for
493 PAXIL CR, at an incidence of 2% or greater for PAXIL CR and were at least twice that reported
494 for placebo: Dizziness, nausea, nervousness, and additional symptoms described by the
495 investigator as associated with tapering or discontinuing PAXIL CR (e.g., emotional lability,
496 headache, agitation, electric shock sensations, fatigue, and sleep disturbances). These events
497 were reported as serious in 0.3% of patients who discontinued therapy with PAXIL CR.

498 During marketing of PAXIL CR and other SSRIs and SNRIs, there have been spontaneous
499 reports of adverse events occurring upon discontinuation of these drugs, (particularly when

500 abrupt), including the following: Dysphoric mood, irritability, agitation, dizziness, sensory
501 disturbances (e.g., paresthesias such as electric shock sensations and tinnitus), anxiety,
502 confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events
503 are generally self-limiting, there have been reports of serious discontinuation symptoms.

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

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

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

516 **Hyponatremia:** Hyponatremia may occur as a result of treatment with SSRIs and SNRIs,
517 including PAXIL CR. In many cases, this hyponatremia appears to be the result of the syndrome
518 of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than
519 110 mmol/L have been reported. Elderly patients may be at greater risk of developing
520 hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise
521 volume depleted may be at greater risk (see PRECAUTIONS: Geriatric Use). Discontinuation of
522 PAXIL CR should be considered in patients with symptomatic hyponatremia and appropriate
523 medical intervention should be instituted.

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

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

537 **Bone Fracture:** Epidemiological studies on bone fracture risk following exposure to some
538 antidepressants, including SSRIs, have reported an association between antidepressant treatment
539 and fractures. There are multiple possible causes for this observation and it is unknown to what

540 extent fracture risk is directly attributable to SSRI treatment. The possibility of a pathological
541 fracture, that is, a fracture produced by minimal trauma in a patient with decreased bone mineral
542 density, should be considered in patients treated with paroxetine who present with unexplained
543 bone pain, point tenderness, swelling, or bruising.

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

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

553 PAXIL CR or the immediate-release formulation has not been evaluated or used to any
554 appreciable extent in patients with a recent history of myocardial infarction or unstable heart
555 disease. Patients with these diagnoses were excluded from clinical studies during premarket
556 testing. Evaluation of electrocardiograms of 682 patients who received immediate-release
557 paroxetine hydrochloride in double-blind, placebo-controlled trials, however, did not indicate
558 that paroxetine is associated with the development of significant ECG abnormalities. Similarly,
559 paroxetine hydrochloride does not cause any clinically important changes in heart rate or blood
560 pressure.

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

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

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

568 Prescribers or other health professionals should inform patients, their families, and their
569 caregivers about the benefits and risks associated with treatment with PAXIL CR and should
570 counsel them in its appropriate use. A patient Medication Guide about “Antidepressant
571 Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions” is
572 available for PAXIL CR. The prescriber or health professional should instruct patients, their
573 families, and their caregivers to read the Medication Guide and should assist them in
574 understanding its contents. Patients should be given the opportunity to discuss the contents of the
575 Medication Guide and to obtain answers to any questions they may have. The complete text of
576 the Medication Guide is reprinted at the end of this document.

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

579 **Clinical Worsening and Suicide Risk:** Patients, their families, and their caregivers

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

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

595 ***Interference With Cognitive and Motor Performance:*** Any psychoactive drug may
596 impair judgment, thinking, or motor skills. Although in controlled studies immediate-release
597 paroxetine hydrochloride has not been shown to impair psychomotor performance, patients
598 should be cautioned about operating hazardous machinery, including automobiles, until they are
599 reasonably certain that therapy with PAXIL CR does not affect their ability to engage in such
600 activities.

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

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

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

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

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

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

615 ***Drug Interactions: Tryptophan:*** As with other serotonin reuptake inhibitors, an interaction
616 between paroxetine and tryptophan may occur when they are coadministered. Adverse
617 experiences, consisting primarily of headache, nausea, sweating, and dizziness, have been
618 reported when tryptophan was administered to patients taking immediate-release paroxetine.
619 Consequently, concomitant use of PAXIL CR with tryptophan is not recommended (see

620 WARNINGS: Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions).

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

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

629 **Serotonergic Drugs:** Based on the mechanism of action of SNRIs and SSRIs, including
630 paroxetine hydrochloride, and the potential for serotonin syndrome, caution is advised when
631 PAXIL CR is coadministered with other drugs that may affect the serotonergic neurotransmitter
632 systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI),
633 lithium, fentanyl, tramadol, or St. John's Wort (see WARNINGS: Serotonin Syndrome or
634 Neuroleptic Malignant Syndrome (NMS)-like Reactions). The concomitant use of PAXIL CR
635 with MAOIs (including linezolid) is contraindicated (see CONTRAINDICATIONS). The
636 concomitant use of PAXIL CR with other SSRIs, SNRIs or tryptophan is not recommended (see
637 PRECAUTIONS: Drug Interactions, *Tryptophan*).

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

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

644 **Triptans:** There have been rare postmarketing reports of serotonin syndrome with the use of
645 an SSRI and a triptan. If concomitant use of PAXIL CR with a triptan is clinically warranted,
646 careful observation of the patient is advised, particularly during treatment initiation and dose
647 increases (see WARNINGS: Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-
648 like Reactions).

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

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

658 **Phenobarbital:** Phenobarbital induces many cytochrome P₄₅₀ (oxidative) enzymes. When a
659 single oral 30-mg dose of immediate-release paroxetine was administered at phenobarbital

660 steady state (100 mg once daily for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an
661 average of 25% and 38%, respectively) compared to paroxetine administered alone. The effect of
662 paroxetine on phenobarbital pharmacokinetics was not studied. Since paroxetine exhibits
663 nonlinear pharmacokinetics, the results of this study may not address the case where the 2 drugs
664 are both being chronically dosed. No initial dosage adjustment with PAXIL CR is considered
665 necessary when coadministered with phenobarbital; any subsequent adjustment should be guided
666 by clinical effect.

667 **Phenytoin:** When a single oral 30-mg dose of immediate-release paroxetine was
668 administered at phenytoin steady state (300 mg once daily for 14 days), paroxetine AUC and $T_{1/2}$
669 were reduced (by an average of 50% and 35%, respectively) compared to immediate-release
670 paroxetine administered alone. In a separate study, when a single oral 300-mg dose of phenytoin
671 was administered at paroxetine steady state (30 mg once daily for 14 days), phenytoin AUC was
672 slightly reduced (12% on average) compared to phenytoin administered alone. Since both drugs
673 exhibit nonlinear pharmacokinetics, the above studies may not address the case where the
674 2 drugs are both being chronically dosed. No initial dosage adjustments are considered necessary
675 when PAXIL CR is coadministered with phenytoin; any subsequent adjustments should be
676 guided by clinical effect (see ADVERSE REACTIONS: Postmarketing Reports).

677 **Drugs Metabolized by CYP2D6:** Many drugs, including most drugs effective in the
678 treatment of major depressive disorder (paroxetine, other SSRIs, and many tricyclics), are
679 metabolized by the cytochrome P₄₅₀ isozyme CYP2D6. Like other agents that are metabolized by
680 CYP2D6, paroxetine may significantly inhibit the activity of this isozyme. In most patients
681 (>90%), this CYP2D6 isozyme is saturated early during paroxetine dosing. In 1 study, daily
682 dosing of immediate-release paroxetine (20 mg once daily) under steady-state conditions
683 increased single-dose desipramine (100 mg) C_{max} , AUC, and $T_{1/2}$ by an average of approximately
684 2-, 5-, and 3-fold, respectively. Concomitant use of paroxetine with risperidone, a CYP2D6
685 substrate has also been evaluated. In 1 study, daily dosing of paroxetine 20 mg in patients
686 stabilized on risperidone (4 to 8 mg/day) increased mean plasma concentrations of risperidone
687 approximately 4-fold, decreased 9-hydroxyrisperidone concentrations approximately 10%, and
688 increased concentrations of the active moiety (the sum of risperidone plus 9-hydroxyrisperidone)
689 approximately 1.4-fold. The effect of paroxetine on the pharmacokinetics of atomoxetine has
690 been evaluated when both drugs were at steady state. In healthy volunteers who were extensive
691 metabolizers of CYP2D6, paroxetine 20 mg daily was given in combination with 20 mg
692 atomoxetine every 12 hours. This resulted in increases in steady state atomoxetine AUC values
693 that were 6- to 8-fold greater and in atomoxetine C_{max} values that were 3- to 4-fold greater than
694 when atomoxetine was given alone. Dosage adjustment of atomoxetine may be necessary and it
695 is recommended that atomoxetine be initiated at a reduced dose when given with paroxetine.

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

699 Therefore, coadministration of PAXIL CR with other drugs that are metabolized by this

700 isozyme, including certain drugs effective in the treatment of major depressive disorder (e.g.,
701 nortriptyline, amitriptyline, imipramine, desipramine, and fluoxetine), phenothiazines,
702 risperidone, tamoxifen, and Type 1C antiarrhythmics (e.g., propafenone, flecainide, and
703 encainide), or that inhibit this enzyme (e.g., quinidine), should be approached with caution.

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

707 Tamoxifen is a pro-drug requiring metabolic activation by CYP2D6. Inhibition of CYP2D6
708 by paroxetine may lead to reduced plasma concentrations of an active metabolite and hence
709 reduced efficacy of tamoxifen.

710 At steady state, when the CYP2D6 pathway is essentially saturated, paroxetine clearance is
711 governed by alternative P₄₅₀ isozymes that, unlike CYP2D6, show no evidence of saturation (see
712 PRECAUTIONS: Tricyclic Antidepressants [TCAs]).

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

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

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

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

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

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

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

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

752 **Procyclidine:** Daily oral dosing of immediate-release paroxetine (30 mg once daily)
753 increased steady-state AUC₀₋₂₄, C_{max}, and C_{min} values of procyclidine (5 mg oral once daily) by
754 35%, 37%, and 67%, respectively, compared to procyclidine alone at steady state. If
755 anticholinergic effects are seen, the dose of procyclidine should be reduced.

756 **Beta-Blockers:** In a study where propranolol (80 mg twice daily) was dosed orally for
757 18 days, the established steady-state plasma concentrations of propranolol were unaltered during
758 coadministration with immediate-release paroxetine (30 mg once daily) for the final 10 days. The
759 effects of propranolol on paroxetine have not been evaluated (see ADVERSE REACTIONS:
760 Postmarketing Reports).

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

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

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

770 **Carcinogenesis, Mutagenesis, Impairment of Fertility: *Carcinogenesis:*** Two-year
771 carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and
772 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to approximately 2
773 (mouse) and 3 (rat) times the (MRHD on a mg/m² basis. There was a significantly greater
774 number of male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50, and
775 4/50 for control, low-, middle-, and high-dose groups, respectively) and a significantly increased
776 linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats.
777 Female rats were not affected. Although there was a dose-related increase in the number of
778 tumors in mice, there was no drug-related increase in the number of mice with tumors. The
779 relevance of these findings to humans is unknown.

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

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

786 A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of
787 15 mg/kg/day, which is approximately twice the MRHD on a mg/m² basis. Irreversible lesions
788 occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks.
789 These lesions consisted of vacuolation of epididymal tubular epithelium at 50 mg/kg/day and
790 atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis at
791 25 mg/kg/day (approximately 8 and 4 times the MRHD on a mg/m² basis).

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

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

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

797 ***Pediatric Use:*** Safety and effectiveness in the pediatric population have not been established
798 (see BOX WARNING and WARNINGS: Clinical Worsening and Suicide Risk). Three placebo-
799 controlled trials in 752 pediatric patients with MDD have been conducted with immediate-
800 release PAXIL, and the data were not sufficient to support a claim for use in pediatric patients.
801 Anyone considering the use of PAXIL CR in a child or adolescent must balance the potential
802 risks with the clinical need.

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

808 Events reported upon discontinuation of treatment with immediate-release paroxetine
809 hydrochloride in the pediatric clinical trials that included a taper phase regimen, which occurred

810 in at least 2% of patients who received immediate-release paroxetine hydrochloride and which
811 occurred at a rate at least twice that of placebo, were: emotional lability (including suicidal
812 ideation, suicide attempt, mood changes, and tearfulness), nervousness, dizziness, nausea, and
813 abdominal pain (see DOSAGE AND ADMINISTRATION: *Discontinuation of Treatment With*
814 *PAXIL CR*).

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

818 In worldwide premarketing clinical trials with immediate-release paroxetine hydrochloride,
819 17% of paroxetine-treated patients (approximately 700) were 65 years or older. Pharmacokinetic
820 studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended;
821 there were, however, no overall differences in the adverse event profile between elderly and
822 younger patients, and effectiveness was similar in younger and older patients (see CLINICAL
823 PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

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

828 **ADVERSE REACTIONS**

829 The information included under the “Adverse Findings Observed in Short-Term,
830 Placebo-Controlled Trials With PAXIL CR” subsection of ADVERSE REACTIONS is based on
831 data from 11 placebo-controlled clinical trials. Three of these studies were conducted in patients
832 with major depressive disorder, 3 studies were done in patients with panic disorder, 1 study was
833 conducted in patients with social anxiety disorder, and 4 studies were done in female patients
834 with PMDD. Two of the studies in major depressive disorder, which enrolled patients in the age
835 range 18 to 65 years, are pooled. Information from a third study of major depressive disorder,
836 which focused on elderly patients (60 to 88 years), is presented separately as is the information
837 from the panic disorder studies and the information from the PMDD studies. Information on
838 additional adverse events associated with PAXIL CR and the immediate-release formulation of
839 paroxetine hydrochloride is included in a separate subsection (see Other Events Observed During
840 the Clinical Development of Paroxetine).

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

843 **Adverse Events Associated With Discontinuation of Treatment: *Major Depressive***
844 ***Disorder*:** Ten percent (21/212) of patients treated with PAXIL CR discontinued treatment due
845 to an adverse event in a pool of 2 studies of patients with major depressive disorder. The most
846 common events ($\geq 1\%$) associated with discontinuation and considered to be drug related (i.e.,
847 those events associated with dropout at a rate approximately twice or greater for PAXIL CR
848 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%

849

850 In a placebo-controlled study of elderly patients with major depressive disorder, 13% (13/104)
851 of patients treated with PAXIL CR discontinued due to an adverse event. Events meeting the
852 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%

853

854 ***Panic Disorder*:** Eleven percent (50/444) of patients treated with PAXIL CR in panic
855 disorder studies discontinued treatment due to an adverse event. Events meeting the above
856 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%

857

858 **Social Anxiety Disorder:** Three percent (5/186) of patients treated with PAXIL CR in the
859 social anxiety disorder study discontinued treatment due to an adverse event. Events meeting the
860 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%

861

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

867 The most common events ($\geq 1\%$) associated with discontinuation in either group treated with
868 PAXIL CR with an incidence rate that is at least twice that of placebo in PMDD trials that
869 employed a continuous dosing regimen are shown in the following table. This table also shows
870 those events that were dose dependent (indicated with an asterisk) as defined as events having an
871 incidence rate with 25 mg of PAXIL CR that was at least twice that with 12.5 mg of PAXIL CR
872 (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%

873 a Events considered to be dose dependent are defined as events having an incidence rate with
874 25 mg of PAXIL CR that was at least twice that with 12.5 mg of PAXIL CR (as well as the
875 placebo group).
876

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

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

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

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

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

897 In the luteal phase dosing PMDD trial, which employed dosing of 12.5 mg/day or 25 mg/day
898 of PAXIL CR limited to the 2 weeks prior to the onset of menses over 3 consecutive menstrual
899 cycles, adverse events were evaluated during the first 14 days of each off-drug phase. When the
900 3 off-drug phases were combined, the following adverse events were reported at an incidence of
901 2% or greater for PAXIL CR and were at least twice the rate of that reported for placebo:
902 Infection (5.3% versus 2.5%), depression (2.8% versus 0.8%), insomnia (2.4% versus 0.8%),
903 sinusitis (2.4% versus 0%), and asthenia (2.0% versus 0.8%).

904 **Incidence in Controlled Clinical Trials:** Table 2 enumerates adverse events that occurred at
905 an incidence of 1% or more among patients treated with PAXIL CR, aged 18 to 65, who
906 participated in 2 short-term (12-week) placebo-controlled trials in major depressive disorder in
907 which patients were dosed in a range of 25 mg to 62.5 mg/day. Table 3 enumerates adverse
908 events reported at an incidence of 5% or greater among elderly patients (ages 60 to 88) treated
909 with PAXIL CR who participated in a short-term (12-week) placebo-controlled trial in major
910 depressive disorder in which patients were dosed in a range of 12.5 mg to 50 mg/day. Table 4
911 enumerates adverse events reported at an incidence of 1% or greater among patients (19 to 72
912 years) treated with PAXIL CR who participated in short-term (10-week) placebo-controlled trials
913 in panic disorder in which patients were dosed in a range of 12.5 mg to 75 mg/day. Table 5
914 enumerates adverse events reported at an incidence of 1% or greater among adult patients treated
915 with PAXIL CR who participated in a short-term (12-week), double-blind, placebo-controlled
916 trial in social anxiety disorder in which patients were dosed in a range of 12.5 to 37.5 mg/day.

917 Table 6 enumerates adverse events that occurred at an incidence of 1% or more among patients
918 treated with PAXIL CR who participated in three, 12-week, placebo-controlled trials in PMDD
919 in which patients were dosed at 12.5 mg/day or 25 mg/day and in one 12-week
920 placebo-controlled trial in which patients were dosed for 2 weeks prior to the onset of menses
921 (luteal phase dosing) at 12.5 mg/day or 25 mg/day. Reported adverse events were classified
922 using a standard COSTART-based Dictionary terminology.

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

930

931 **Table 2. Treatment-Emergent Adverse Events Occurring in $\geq 1\%$ of Patients Treated With**
932 **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%
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%

- 933 a. Adverse events for which the PAXIL CR reporting incidence was less than or equal to the
934 placebo incidence are not included. These events are: Abnormal dreams, anxiety, arthralgia,
935 depersonalization, dysmenorrhea, dyspepsia, hyperkinesia, increased appetite, myalgia,
936 nervousness, pharyngitis, purpura, rash, respiratory disorder, sinusitis, urinary frequency, and
937 weight gain.
- 938 b. <1% means greater than zero and less than 1%.
- 939 c. Mostly flu.
- 940 d. A wide variety of injuries with no obvious pattern.
- 941 e. Pain in a variety of locations with no obvious pattern.
- 942 f. Most frequently seasonal allergic symptoms.
- 943 g. Usually flushing.
- 944 h. Mostly blurred vision.
- 945 i. Based on the number of males or females.
- 946 j. Mostly anorgasmia or delayed ejaculation.
- 947 k. Mostly anorgasmia or delayed orgasm.

948

949 **Table 3. Treatment-Emergent Adverse Events Occurring in $\geq 5\%$ of**
 950 **Patients Treated With PAXIL CR in a Study of Elderly Patients With Major Depressive**
 951 **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%

952 a. Adverse events for which the PAXIL CR reporting incidence was less than or equal to the
 953 placebo incidence are not included. These events are nausea and respiratory disorder.

954 b. <1% means greater than zero and less than 1%.

955 c. Based on the number of males.

956 d. Mostly anorgasmia or delayed ejaculation.

957

958 **Table 4. Treatment-Emergent Adverse Events Occurring in ≥1% of Patients Treated With**
959 **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%

- 960 a. Adverse events for which the reporting rate for PAXIL CR was less than or equal to the
961 placebo rate are not included. These events are: Abnormal dreams, allergic reaction, back
962 pain, bronchitis, chest pain, concentration impaired, confusion, cough increased, depression,
963 dizziness, dysmenorrhea, dyspepsia, fever, flatulence, headache, increased appetite, infection,
964 menstrual disorder, migraine, pain, paresthesia, pharyngitis, respiratory disorder, rhinitis,
965 tachycardia, taste perversion, thinking abnormal, urinary tract infection, and vomiting.
966 b. <1% means greater than zero and less than 1%.
967 c. Various physical injuries.
968 d. Mostly flushing.
969 e. Mostly muscle tightness or stiffness.
970 f. Mostly blurred vision.
971 g. Based on the number of male patients.
972 h. Mostly anorgasmia or delayed ejaculation.
973 i. Based on the number of female patients.
974 j. Mostly anorgasmia or difficulty achieving orgasm.
975

976 **Table 5. Treatment-Emergent Adverse Effects Occurring in ≥1% of Patients Treated**
977 **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%

- 978 a. Adverse events for which the reporting rate for PAXIL CR was less than or equal to the
979 placebo rate are not included. These events are: Dysmenorrhea, flatulence, gastroenteritis,
980 hypertonia, infection, pain, pharyngitis, rash, respiratory disorder, rhinitis, and vomiting.
- 981 b. <1% means greater than zero and less than 1%.
- 982 c. Various physical injuries.
- 983 d. Most frequently seasonal allergic symptoms.
- 984 e. Mostly blurred vision.
- 985 f. Based on the number of male patients.
- 986 g. Mostly anorgasmia or delayed ejaculation.
- 987 h. Based on the number of female patients.
- 988 i. Mostly anorgasmia or difficulty achieving orgasm.

989

990 **Table 6. Treatment-Emergent Adverse Events Occurring in ≥1% of Patients Treated With**
 991 **PAXIL CR in a Pool of 3 Premenstrual Dysphoric Disorder Studies With Continuous**
 992 **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%

- 993 a. Adverse events for which the reporting rate of PAXIL CR was less than or equal to the
994 placebo rate are not included. These events for continuous dosing are: Abdominal pain, back
995 pain, pain, trauma, weight gain, myalgia, pharyngitis, respiratory disorder, rhinitis, sinusitis,
996 pruritis, dysmenorrhea, menstrual disorder, urinary tract infection, and vomiting. The events
997 for luteal phase dosing are: Allergic reaction, back pain, headache, infection, pain, trauma,
998 myalgia, anxiety, pharyngitis, respiratory disorder, cystitis, and dysmenorrhea.
999 b. <1% means greater than zero and less than 1%.
- 1000 c. The luteal phase and continuous dosing PMDD trials were not designed for making direct
1001 comparisons between the 2 dosing regimens. Therefore, a comparison between the 2 dosing
1002 regimens of the PMDD trials of incidence rates shown in Table 6 should be avoided.
- 1003 d. Mostly anorgasmia or difficulty achieving orgasm.

1004
1005
1006
1007
1008

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

1009 **Table 7. Incidence of Common Adverse Events in Placebo, 12.5 mg, and 25 mg of**
1010 **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%

1011

1012 A comparison of adverse event rates in a fixed-dose study comparing immediate-release
1013 paroxetine with placebo in the treatment of major depressive disorder revealed a clear dose
1014 dependency for some of the more common adverse events associated with the use of
1015 immediate-release paroxetine.

1016 **Male and Female Sexual Dysfunction With SSRIs:** Although changes in sexual desire,
1017 sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric
1018 disorder, they may also be a consequence of pharmacologic treatment. In particular, some
1019 evidence suggests that SSRIs can cause such untoward sexual experiences.

1020 Reliable estimates of the incidence and severity of untoward experiences involving sexual
1021 desire, performance, and satisfaction are difficult to obtain; however, in part because patients and
1022 physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of
1023 untoward sexual experience and performance cited in product labeling, are likely to
1024 underestimate their actual incidence.

1025 The percentage of patients reporting symptoms of sexual dysfunction in the pool of 2
1026 placebo-controlled trials in nonelderly patients with major depressive disorder, in the pool of 3
1027 placebo-controlled trials in patients with panic disorder, in the placebo-controlled trial in patients
1028 with social anxiety disorder, and in the intermittent dosing and the pool of 3 placebo-controlled
1029 continuous dosing trials in female patients with PMDD are as follows:

1030

	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%

1031

1032 There are no adequate, controlled studies examining sexual dysfunction with paroxetine
1033 treatment.

1034 Paroxetine treatment has been associated with several cases of priapism. In those cases with a
1035 known outcome, patients recovered without sequelae.

1036 While it is difficult to know the precise risk of sexual dysfunction associated with the use of
1037 SSRIs, physicians should routinely inquire about such possible side effects.

1038 **Weight and Vital Sign Changes:** Significant weight loss may be an undesirable result of
1039 treatment with paroxetine for some patients but, on average, patients in controlled trials with
1040 PAXIL CR or the immediate-release formulation, had minimal weight loss (about 1 pound). No
1041 significant changes in vital signs (systolic and diastolic blood pressure, pulse, and temperature)
1042 were observed in patients treated with PAXIL CR, or immediate-release paroxetine
1043 hydrochloride, in controlled clinical trials.

1044 **ECG Changes:** In an analysis of ECGs obtained in 682 patients treated with
1045 immediate-release paroxetine and 415 patients treated with placebo in controlled clinical trials,
1046 no clinically significant changes were seen in the ECGs of either group.

1047 **Liver Function Tests:** In a pool of 2 placebo-controlled clinical trials, patients treated with
1048 PAXIL CR or placebo exhibited abnormal values on liver function tests at comparable rates. In
1049 particular, the controlled-release paroxetine-versus-placebo comparisons for alkaline
1050 phosphatase, SGOT, SGPT, and bilirubin revealed no differences in the percentage of patients
1051 with marked abnormalities.

1052 In a study of elderly patients with major depressive disorder, 3 of 104 patients treated with
1053 PAXIL CR and none of 109 placebo patients experienced liver transaminase elevations of
1054 potential clinical concern.

1055 Two of the patients treated with PAXIL CR dropped out of the study due to abnormal liver
1056 function tests; the third patient experienced normalization of transaminase levels with continued
1057 treatment. Also, in the pool of 3 studies of patients with panic disorder, 4 of 444 patients treated
1058 with PAXIL CR and none of 445 placebo patients experienced liver transaminase elevations of
1059 potential clinical concern. Elevations in all 4 patients decreased substantially after
1060 discontinuation of PAXIL CR. The clinical significance of these findings is unknown.

1061 In placebo-controlled clinical trials with the immediate-release formulation of paroxetine,
1062 patients exhibited abnormal values on liver function tests at no greater rate than that seen in
1063 placebo-treated patients.

1064 **Hallucinations:** In pooled clinical trials of immediate-release paroxetine hydrochloride,
1065 hallucinations were observed in 22 of 9,089 patients receiving drug and in 4 of 3,187 patients
1066 receiving placebo.

1067 **Other Events Observed During the Clinical Development of Paroxetine:** The
1068 following adverse events were reported during the clinical development of PAXIL CR and/or the
1069 clinical development of the immediate-release formulation of paroxetine.

1070 Adverse events for which frequencies are provided below occurred in clinical trials with the
1071 controlled-release formulation of paroxetine. During its premarketing assessment in major
1072 depressive disorder, panic disorder, social anxiety disorder, and PMDD, multiple doses of
1073 PAXIL CR were administered to 1,627 patients in phase 3 double-blind, controlled, outpatient
1074 studies. Untoward events associated with this exposure were recorded by clinical investigators
1075 using terminology of their own choosing. Consequently, it is not possible to provide a
1076 meaningful estimate of the proportion of individuals experiencing adverse events without first
1077 grouping similar types of untoward events into a smaller number of standardized event
1078 categories.

1079 In the tabulations that follow, reported adverse events were classified using a
1080 COSTART-based dictionary. The frequencies presented, therefore, represent the proportion of
1081 the 1,627 patients exposed to PAXIL CR who experienced an event of the type cited on at least 1
1082 occasion while receiving PAXIL CR. All reported events are included except those already listed
1083 in Tables 2 through 7 and those events where a drug cause was remote. If the COSTART term
1084 for an event was so general as to be uninformative, it was deleted or, when possible, replaced
1085 with a more informative term. It is important to emphasize that although the events reported
1086 occurred during treatment with paroxetine, they were not necessarily caused by it.

1087 Events are further categorized by body system and listed in order of decreasing frequency
1088 according to the following definitions: Frequent adverse events are those occurring on 1 or more
1089 occasions in at least 1/100 patients (only those not already listed in the tabulated results from
1090 placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in
1091 1/100 to 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients.

1092 Adverse events for which frequencies are not provided occurred during the premarketing
1093 assessment of immediate-release paroxetine in phase 2 and 3 studies of major depressive
1094 disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized

1095 anxiety disorder, and posttraumatic stress disorder. The conditions and duration of exposure to
1096 immediate-release paroxetine varied greatly and included (in overlapping categories) open and
1097 double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and
1098 fixed-dose and titration studies. Only those events not previously listed for controlled-release
1099 paroxetine are included. The extent to which these events may be associated with PAXIL CR is
1100 unknown.

1101 Events are listed alphabetically within the respective body system. Events of major clinical
1102 importance are also described in the PRECAUTIONS section.

1103 **Body as a Whole:** Infrequent were chills, face edema, fever, flu syndrome, malaise; rare
1104 were abscess, anaphylactoid reaction, anticholinergic syndrome, hypothermia; also observed
1105 were adrenergic syndrome, neck rigidity, sepsis.

1106 **Cardiovascular System:** Infrequent were angina pectoris, bradycardia, hematoma,
1107 hypertension, hypotension, palpitation, postural hypotension, supraventricular tachycardia,
1108 syncope; rare were bundle branch block; also observed were arrhythmia nodal, atrial fibrillation,
1109 cerebrovascular accident, congestive heart failure, low cardiac output, myocardial infarct,
1110 myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles,
1111 thrombophlebitis, thrombosis, vascular headache, ventricular extrasystoles.

1112 **Digestive System:** Infrequent were bruxism, dysphagia, eructation, gastritis,
1113 gastroenteritis, gastroesophageal reflux, gingivitis, hemorrhoids, liver function test abnormal,
1114 melena, pancreatitis, rectal hemorrhage, toothache, ulcerative stomatitis; rare were colitis,
1115 glossitis, gum hyperplasia, hepatosplenomegaly, increased salivation, intestinal obstruction,
1116 peptic ulcer, stomach ulcer, throat tightness; also observed were aphthous stomatitis, bloody
1117 diarrhea, bulimia, cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions,
1118 fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, jaundice, mouth
1119 ulceration, salivary gland enlargement, sialadenitis, stomatitis, tongue discoloration, tongue
1120 edema.

1121 **Endocrine System:** Infrequent were ovarian cyst, testes pain; rare were diabetes mellitus,
1122 hyperthyroidism; also observed were goiter, hypothyroidism, thyroiditis.

1123 **Hemic and Lymphatic System:** Infrequent were anemia, eosinophilia, hypochromic
1124 anemia, leukocytosis, leukopenia, lymphadenopathy, purpura; rare were thrombocytopenia; also
1125 observed were anisocytosis, basophilia, bleeding time increased, lymphedema, lymphocytosis,
1126 lymphopenia, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia.

1127 **Metabolic and Nutritional Disorders:** Infrequent were generalized edema,
1128 hyperglycemia, hypokalemia, peripheral edema, SGOT increased, SGPT increased, thirst; rare
1129 were bilirubinemia, dehydration, hyperkalemia, obesity; also observed were alkaline phosphatase
1130 increased, BUN increased, creatinine phosphokinase increased, gamma globulins increased,
1131 gout, hypercalcemia, hypercholesteremia, hyperphosphatemia, hypocalcemia, hypoglycemia,
1132 hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased.

1133 **Musculoskeletal System:** Infrequent were arthritis, bursitis, tendonitis; rare were
1134 myasthenia, myopathy, myositis; also observed were generalized spasm, osteoporosis,

1135 tenosynovitis, tetany.

1136 **Nervous System:** Frequent were depression; infrequent were amnesia, convulsion,
1137 depersonalization, dystonia, emotional lability, hallucinations, hyperkinesia, hypesthesia,
1138 hypokinesia, incoordination, libido increased, neuralgia, neuropathy, nystagmus, paralysis,
1139 vertigo; rare were ataxia, coma, diplopia, dyskinesia, hostility, paranoid reaction, torticollis,
1140 withdrawal syndrome; also observed were abnormal gait, akathisia, akinesia, aphasia,
1141 choreoathetosis, circumoral paresthesia, delirium, delusions, dysarthria, euphoria, extrapyramidal
1142 syndrome, fasciculations, grand mal convulsion, hyperalgesia, irritability, manic reaction,
1143 manic-depressive reaction, meningitis, myelitis, peripheral neuritis, psychosis, psychotic
1144 depression, reflexes decreased, reflexes increased, stupor, trismus.

1145 **Respiratory System:** Frequent were pharyngitis; infrequent were asthma, dyspnea,
1146 epistaxis, laryngitis, pneumonia; rare were stridor; also observed were dysphonia, emphysema,
1147 hemoptysis, hiccups, hyperventilation, lung fibrosis, pulmonary edema, respiratory flu, sputum
1148 increased.

1149 **Skin and Appendages:** Frequent were rash; infrequent were acne, alopecia, dry skin,
1150 eczema, pruritus, urticaria; rare were exfoliative dermatitis, furunculosis, pustular rash,
1151 seborrhea; also observed were angioedema, ecchymosis, erythema multiforme, erythema
1152 nodosum, hirsutism, maculopapular rash, skin discoloration, skin hypertrophy, skin ulcer,
1153 sweating decreased, vesiculobullous rash.

1154 **Special Senses:** Infrequent were conjunctivitis, earache, keratoconjunctivitis, mydriasis,
1155 photophobia, retinal hemorrhage, tinnitus; rare were blepharitis, visual field defect; also observed
1156 were amblyopia, anisocoria, blurred vision, cataract, conjunctival edema, corneal ulcer, deafness,
1157 exophthalmos, glaucoma, hyperacusis, night blindness, parosmia, ptosis, taste loss.

1158 **Urogenital System:** Frequent were dysmenorrhea^{*}; infrequent were albuminuria,
1159 amenorrhea^{*}, breast pain^{*}, cystitis, dysuria, prostatitis^{*}, urinary retention; rare were breast
1160 enlargement^{*}, breast neoplasm^{*}, female lactation, hematuria, kidney calculus, metrorrhagia^{*},
1161 nephritis, nocturia, pregnancy and puerperal disorders^{*}, salpingitis, urinary incontinence, uterine
1162 fibroids enlarged^{*}; also observed were breast atrophy, ejaculatory disturbance, endometrial
1163 disorder, epididymitis, fibrocystic breast, leukorrhea, mastitis, oliguria, polyuria, pyuria,
1164 urethritis, urinary casts, urinary urgency, urolith, uterine spasm, vaginal hemorrhage.

1165 ^{*}Based on the number of men and women as appropriate.

1166 **Postmarketing Reports:** Voluntary reports of adverse events in patients taking
1167 immediate-release paroxetine hydrochloride that have been received since market introduction
1168 and not listed above that may have no causal relationship with the drug include acute
1169 pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis,
1170 and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré
1171 syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion,
1172 symptoms suggestive of prolactinemia and galactorrhea; extrapyramidal symptoms which have
1173 included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which
1174 has been associated with concomitant use of pimozide; tremor and trismus; status epilepticus,

1175 acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia,
1176 laryngismus, optic neuritis, porphyria, restless legs syndrome (RLS), ventricular fibrillation,
1177 ventricular tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia,
1178 events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow
1179 aplasia, and agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura).
1180 There has been a case report of an elevated phenytoin level after 4 weeks of immediate-release
1181 paroxetine and phenytoin coadministration. There has been a case report of severe hypotension
1182 when immediate-release paroxetine was added to chronic metoprolol treatment.

1183 **DRUG ABUSE AND DEPENDENCE**

1184 **Controlled Substance Class:** PAXIL CR is not a controlled substance.

1185 **Physical and Psychologic Dependence:** PAXIL CR has not been systematically studied
1186 in animals or humans for its potential for abuse, tolerance or physical dependence. While the
1187 clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were
1188 not systematic and it is not possible to predict on the basis of this limited experience the extent to
1189 which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently,
1190 patients should be evaluated carefully for history of drug abuse, and such patients should be
1191 observed closely for signs of misuse or abuse of PAXIL CR (e.g., development of tolerance,
1192 incrementations of dose, drug-seeking behavior).

1193 **OVERDOSAGE**

1194 **Human Experience:** Since the introduction of immediate-release paroxetine hydrochloride in
1195 the United States, 342 spontaneous cases of deliberate or accidental overdose during
1196 paroxetine treatment have been reported worldwide (circa 1999). These include overdoses with
1197 paroxetine alone and in combination with other substances. Of these, 48 cases were fatal and of
1198 the fatalities, 17 appeared to involve paroxetine alone. Eight fatal cases that documented the
1199 amount of paroxetine ingested were generally confounded by the ingestion of other drugs or
1200 alcohol or the presence of significant comorbid conditions. Of 145 non-fatal cases with known
1201 outcome, most recovered without sequelae. The largest known ingestion involved 2,000 mg of
1202 paroxetine (33 times the maximum recommended daily dose) in a patient who recovered.

1203 Commonly reported adverse events associated with paroxetine overdose include
1204 somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other
1205 notable signs and symptoms observed with overdoses involving paroxetine (alone or with other
1206 substances) include mydriasis, convulsions (including status epilepticus), ventricular
1207 dysrhythmias (including torsade de pointes), hypertension, aggressive reactions, syncope,
1208 hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction
1209 (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin
1210 syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

1211 **Overdosage Management:** No specific antidotes for paroxetine are known. Treatment
1212 should consist of those general measures employed in the management of overdose with any
1213 drugs effective in the treatment of major depressive disorder.

1214 Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital
1215 signs. General supportive and symptomatic measures are also recommended. Induction of emesis
1216 is not recommended. Due to the large volume of distribution of this drug, forced diuresis,
1217 dialysis, hemoperfusion, or exchange perfusion are unlikely to be of benefit.

1218 A specific caution involves patients taking or recently having taken paroxetine who might
1219 ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the
1220 parent tricyclic and an active metabolite may increase the possibility of clinically significant
1221 sequelae and extend the time needed for close medical observation (see PRECAUTIONS: *Drugs*
1222 *Metabolized by Cytochrome CYP2D6*).

1223 In managing overdose, consider the possibility of multiple drug involvement. The physician
1224 should consider contacting a poison control center for additional information on the treatment of
1225 any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians'*
1226 *Desk Reference* (PDR).

1227 **DOSAGE AND ADMINISTRATION**

1228 **Major Depressive Disorder: Usual Initial Dosage:** PAXIL CR should be administered as
1229 a single daily dose, usually in the morning, with or without food. The recommended initial dose
1230 is 25 mg/day. Patients were dosed in a range of 25 mg to 62.5 mg/day in the clinical trials
1231 demonstrating the effectiveness of PAXIL CR in the treatment of major depressive disorder. As
1232 with all drugs effective in the treatment of major depressive disorder, the full effect may be
1233 delayed. Some patients not responding to a 25-mg dose may benefit from dose increases, in
1234 12.5-mg/day increments, up to a maximum of 62.5 mg/day. Dose changes should occur at
1235 intervals of at least 1 week.

1236 Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be
1237 swallowed whole.

1238 **Maintenance Therapy:** There is no body of evidence available to answer the question of
1239 how long the patient treated with PAXIL CR should remain on it. It is generally agreed that acute
1240 episodes of major depressive disorder require several months or longer of sustained
1241 pharmacologic therapy. Whether the dose of an antidepressant needed to induce remission is
1242 identical to the dose needed to maintain and/or sustain euthymia is unknown.

1243 Systematic evaluation of the efficacy of immediate-release paroxetine hydrochloride has
1244 shown that efficacy is maintained for periods of up to 1 year with doses that averaged about
1245 30 mg, which corresponds to a 37.5-mg dose of PAXIL CR, based on relative bioavailability
1246 considerations (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

1247 **Panic Disorder: Usual Initial Dosage:** PAXIL CR should be administered as a single daily
1248 dose, usually in the morning. Patients should be started on 12.5 mg/day. Dose changes should
1249 occur in 12.5-mg/day increments and at intervals of at least 1 week. Patients were dosed in a
1250 range of 12.5 to 75 mg/day in the clinical trials demonstrating the effectiveness of PAXIL CR.
1251 The maximum dosage should not exceed 75 mg/day.

1252 Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be

1253 swallowed whole.

1254 **Maintenance Therapy:** Long-term maintenance of efficacy with the immediate-release
1255 formulation of paroxetine was demonstrated in a 3-month relapse prevention trial. In this trial,
1256 patients with panic disorder assigned to immediate-release paroxetine demonstrated a lower
1257 relapse rate compared to patients on placebo. Panic disorder is a chronic condition, and it is
1258 reasonable to consider continuation for a responding patient. Dosage adjustments should be
1259 made to maintain the patient on the lowest effective dosage, and patients should be periodically
1260 reassessed to determine the need for continued treatment.

1261 **Social Anxiety Disorder: Usual Initial Dosage:** PAXIL CR should be administered as a
1262 single daily dose, usually in the morning, with or without food. The recommended initial dose is
1263 12.5 mg/day. Patients were dosed in a range of 12.5 mg to 37.5 mg/day in the clinical trial
1264 demonstrating the effectiveness of PAXIL CR in the treatment of social anxiety disorder. If the
1265 dose is increased, this should occur at intervals of at least 1 week, in increments of 12.5 mg/day,
1266 up to a maximum of 37.5 mg/day.

1267 Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be
1268 swallowed whole.

1269 **Maintenance Therapy:** There is no body of evidence available to answer the question of
1270 how long the patient treated with PAXIL CR should remain on it. Although the efficacy of
1271 PAXIL CR beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials,
1272 social anxiety disorder is recognized as a chronic condition, and it is reasonable to consider
1273 continuation of treatment for a responding patient. Dosage adjustments should be made to
1274 maintain the patient on the lowest effective dosage, and patients should be periodically
1275 reassessed to determine the need for continued treatment.

1276 **Premenstrual Dysphoric Disorder: Usual Initial Dosage:** PAXIL CR should be
1277 administered as a single daily dose, usually in the morning, with or without food. PAXIL CR
1278 may be administered either daily throughout the menstrual cycle or limited to the luteal phase of
1279 the menstrual cycle, depending on physician assessment. The recommended initial dose is
1280 12.5 mg/day. In clinical trials, both 12.5 mg/day and 25 mg/day were shown to be effective.
1281 Dose changes should occur at intervals of at least 1 week.

1282 Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be
1283 swallowed whole.

1284 **Maintenance/Continuation Therapy:** The effectiveness of PAXIL CR for a period
1285 exceeding 3 menstrual cycles has not been systematically evaluated in controlled trials.
1286 However, women commonly report that symptoms worsen with age until relieved by the onset of
1287 menopause. Therefore, it is reasonable to consider continuation of a responding patient. Patients
1288 should be periodically reassessed to determine the need for continued treatment.

1289 **Special Populations: Treatment of Pregnant Women During the Third Trimester:**
1290 Neonates exposed to PAXIL CR and other SSRIs or SNRIs, late in the third trimester have
1291 developed complications requiring prolonged hospitalization, respiratory support, and tube
1292 feeding (see WARNINGS: Usage in Pregnancy). When treating pregnant women with paroxetine

1293 during the third trimester, the physician should carefully consider the potential risks and benefits
1294 of treatment. The physician may consider tapering paroxetine in the third trimester.

1295 **Dosage for Elderly or Debilitated Patients, and Patients With Severe Renal or**
1296 **Hepatic Impairment:** The recommended initial dose of PAXIL CR is 12.5 mg/day for elderly
1297 patients, debilitated patients, and/or patients with severe renal or hepatic impairment. Increases
1298 may be made if indicated. Dosage should not exceed 50 mg/day.

1299 **Switching Patients to or From a Monoamine Oxidase Inhibitor:** At least 14 days
1300 should elapse between discontinuation of an MAOI and initiation of therapy with PAXIL CR.
1301 Similarly, at least 14 days should be allowed after stopping PAXIL CR before starting an MAOI.

1302 **Discontinuation of Treatment With PAXIL CR:** Symptoms associated with discontinuation
1303 of immediate-release paroxetine hydrochloride or PAXIL CR have been reported (see
1304 PRECAUTIONS: Discontinuation of Treatment with PAXIL CR). Patients should be monitored
1305 for these symptoms when discontinuing treatment, regardless of the indication for which PAXIL
1306 CR is being prescribed. A gradual reduction in the dose rather than abrupt cessation is
1307 recommended whenever possible. If intolerable symptoms occur following a decrease in the dose
1308 or upon discontinuation of treatment, then resuming the previously prescribed dose may be
1309 considered. Subsequently, the physician may continue decreasing the dose but at a more gradual
1310 rate.

1311 **HOW SUPPLIED**

1312 PAXIL CR is supplied as an enteric film-coated, controlled-release, round tablet, as follows:

1313 12.5-mg yellow tablets, engraved with PAXIL CR and 12.5

1314 NDC 0029-3206-13 Bottles of 30

1315 25-mg pink tablets, engraved with PAXIL CR and 25

1316 NDC 0029-3207-13 Bottles of 30

1317 37.5 mg blue tablets, engraved with PAXIL CR and 37.5

1318 NDC 0029-3208-13 Bottles of 30

1319 Store at or below 25°C (77°F) [see USP].

1320

1321 PAXIL CR is a registered trademark of GlaxoSmithKline.

1322 GEOMATRIX is a trademark of Jago Pharma, Muttenz, Switzerland.

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Medication Guide

1325

Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal

1326

Thoughts or Actions

1327

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

1328

1329

Read the Medication Guide that comes with your or your family member's antidepressant

1330

medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with

1331

antidepressant medicines. **Talk to your, or your family member's, healthcare provider**

1332

about:

1333

- All risks and benefits of treatment with antidepressant medicines

1334

- All treatment choices for depression or other serious mental illness

1335

1336

What is the most important information I should know about antidepressant medicines,

1337

depression and other serious mental illnesses, and suicidal thoughts or action?

1338

1339

1. Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.

1340

1341

1342

2. Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.

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1347

3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?

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1349

1350

- Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.

1351

1352

1353

- Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.

1354

1355

- Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

1356

1357

1358

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

1359

1360

1361

- Thoughts about suicide or dying

1362

- Attempts to commit suicide

1363

- New or worse depression

- 1364 • New or worse anxiety
- 1365 • Feeling very agitated or restless
- 1366 • Panic attacks
- 1367 • Trouble sleeping (insomnia)
- 1368 • New or worse irritability
- 1369 • Acting aggressive, being angry, or violent
- 1370 • Acting on dangerous impulses
- 1371 • An extreme increase in activity and talking (mania)
- 1372 • Other unusual changes in behavior or mood

1373

1374 **What else do I need to know about antidepressant medicines?**

1375

- 1376 • **Never stop an antidepressant medicine without first talking to a healthcare**
- 1377 **provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.

1378

- 1379 • **Antidepressants are medicines used to treat depression and other illnesses.** It is
- 1380 important to discuss all the risks of treating depression and also the risks of not treating it.
- 1381 Patients and their families or other caregivers should discuss all treatment choices with
- 1382 the healthcare provider, not just the use of antidepressants.

1383

- 1384 • **Antidepressant medicines have other side effects.** Call your doctor for medical advice
- 1385 about side effects. You may report side effects to FDA at 1-800-FDA-1088.

1386

- 1387 • **Antidepressant medicines can interact with other medicines.** Know all of the
- 1388 medicines that you or your family member takes. Keep a list of all medicines to show the
- 1389 healthcare provider. Do not start new medicines without first checking with your
- 1390 healthcare provider.

1391

- 1392 • **Not all antidepressant medicines prescribed for children are FDA approved for use**
- 1393 **in children.** Talk to your child's healthcare provider for more information.

1394

1395 This Medication Guide has been approved by the U.S. Food and Drug Administration for all

1396 antidepressants.

1397

1398 January 2008

PCR:3MG

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1401

GlaxoSmithKline

1402 Research Triangle Park, NC 27709

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1405

1406 Month Year

PCR:XXPI