

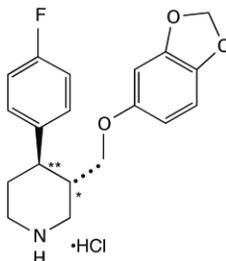
PAXIL CR[®]
(paroxetine hydrochloride)
Controlled-Release Tablets

Suicidality and Antidepressant Drugs

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

DESCRIPTION

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



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

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

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

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

42 **CLINICAL PHARMACOLOGY**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

128 **Clinical Trials**

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

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

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

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

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

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

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

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

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

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

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

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

202 **INDICATIONS AND USAGE**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

283 **CONTRAINDICATIONS**

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

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

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

290 **WARNINGS**

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

305 The pooled analyses of placebo-controlled trials in children and adolescents with MDD,
306 obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-
307 term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-
308 controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-
309 term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients.
310 There was considerable variation in risk of suicidality among drugs, but a tendency toward an

311 increase in the younger patients for almost all drugs studied. There were differences in absolute
 312 risk of suicidality across the different indications, with the highest incidence in MDD. The risk
 313 differences (drug vs placebo), however, were relatively stable within age strata and across
 314 indications. These risk differences (drug-placebo difference in the number of cases of suicidality
 315 per 1,000 patients treated) are provided in Table 1.

316 **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

317
 318 No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but
 319 the number was not sufficient to reach any conclusion about drug effect on suicide.

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

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

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

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

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

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

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

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

372 **Serotonin Syndrome:** The development of a potentially life-threatening serotonin
373 syndrome may occur with SNRIs and SSRIs, including PAXIL CR, particularly with
374 concomitant use of serotonergic drugs (including triptans) and with drugs which impair
375 metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include
376 mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g.,
377 tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g.,
378 hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting,
379 diarrhea).

380 The concomitant use of PAXIL CR with MAOIs intended to treat depression is
381 contraindicated (see CONTRAINDICATIONS and WARNINGS—Potential for
382 Interaction With Monoamine Oxidase Inhibitors).

383 **If concomitant treatment with PAXIL CR with a 5-hydroxytryptamine receptor agonist**
384 **(triptan) is clinically warranted, careful observation of the patient is advised, particularly**
385 **during treatment initiation and dose increases (see PRECAUTIONS—Drug Interactions).**

386 **The concomitant use of PAXIL CR with serotonin precursors (such as tryptophan) is**
387 **not recommended (see PRECAUTIONS—Drug Interactions).**

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

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

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

- 400 • A study based on Swedish national registry data demonstrated that infants exposed to
401 paroxetine during pregnancy (n = 815) had an increased risk of cardiovascular
402 malformations (2% risk in paroxetine-exposed infants) compared to the entire registry
403 population (1% risk), for an odds ratio (OR) of 1.8 (95% confidence interval 1.1 to 2.8).
404 No increase in the risk of overall congenital malformations was seen in the paroxetine-
405 exposed infants. The cardiac malformations in the paroxetine-exposed infants were
406 primarily ventricular septal defects (VSDs) and atrial septal defects (ASDs). Septal
407 defects range in severity from those that resolve spontaneously to those which require
408 surgery.
- 409 • A separate retrospective cohort study from the United States (United Healthcare data)
410 evaluated 5,956 infants of mothers dispensed antidepressants during the first trimester
411 (n = 815 for paroxetine). This study showed a trend towards an increased risk for
412 cardiovascular malformations for paroxetine (risk of 1.5%) compared to other
413 antidepressants (risk of 1%), for an OR of 1.5 (95% confidence interval 0.8 to 2.9). Of
414 the 12 paroxetine-exposed infants with cardiovascular malformations, 9 had VSDs.
415 This study also suggested an increased risk of overall major congenital malformations
416 including cardiovascular defects for paroxetine (4% risk) compared to other (2% risk)
417 antidepressants (OR 1.8; 95% confidence interval 1.2 to 2.8).
- 418 • Two large case-control studies using separate databases, each with >9,000 birth defect
419 cases and >4,000 controls, found that maternal use of paroxetine during the first
420 trimester of pregnancy was associated with a 2- to 3-fold increased risk of right
421 ventricular outflow tract obstructions. In one study the OR was 2.5 (95% confidence
422 interval, 1.0 to 6.0, 7 exposed infants) and in the other study the OR was 3.3 (95%

423 confidence interval, 1.3 to 8.8, 6 exposed infants).

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

437 If a patient becomes pregnant while taking paroxetine, she should be advised of the potential
438 harm to the fetus. Unless the benefits of paroxetine to the mother justify continuing treatment,
439 consideration should be given to either discontinuing paroxetine therapy or switching to another
440 antidepressant (see PRECAUTIONS—Discontinuation of Treatment with PAXIL CR). For
441 women who intend to become pregnant or are in their first trimester of pregnancy, paroxetine
442 should only be initiated after consideration of the other available treatment options.

443 **Animal Findings:** Reproduction studies were performed at doses up to 50 mg/kg/day in rats
444 and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately
445 8 (rat) and 2 (rabbit) times the maximum recommended human dose (MRHD) on an mg/m²
446 basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was
447 an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last
448 trimester of gestation and continued throughout lactation. This effect occurred at a dose of
449 1 mg/kg/day or approximately one-sixth of the MRHD on an mg/m² basis. The no-effect dose for
450 rat pup mortality was not determined. The cause of these deaths is not known.

451 **Nonteratogenic Effects:** Neonates exposed to PAXIL CR and other SSRIs or serotonin
452 and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed
453 complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such
454 complications can arise immediately upon delivery. Reported clinical findings have included
455 respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty,
456 vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and
457 constant crying. These features are consistent with either a direct toxic effect of SSRIs and
458 SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the
459 clinical picture is consistent with serotonin syndrome (see WARNINGS—Potential for
460 Interaction With Monoamine Oxidase Inhibitors).

461 Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent
462 pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 – 2 per 1,000 live births in

463 the general population and is associated with substantial neonatal morbidity and mortality. In a
464 retrospective case-control study of 377 women whose infants were born with PPHN and 836
465 women whose infants were born healthy, the risk for developing PPHN was approximately six-
466 fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who
467 had not been exposed to antidepressants during pregnancy. There is currently no corroborative
468 evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first
469 study that has investigated the potential risk. The study did not include enough cases with
470 exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk.

471 There have also been postmarketing reports of premature births in pregnant women exposed
472 to paroxetine or other SSRIs.

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

479 **PRECAUTIONS**

480 **General: Activation of Mania/Hypomania:** During premarketing testing of
481 immediate-release paroxetine hydrochloride, hypomania or mania occurred in approximately
482 1.0% of paroxetine-treated unipolar patients compared to 1.1% of active-control and 0.3% of
483 placebo-treated unipolar patients. In a subset of patients classified as bipolar, the rate of manic
484 episodes was 2.2% for immediate-release paroxetine and 11.6% for the combined active-control
485 groups. Among 1,627 patients with major depressive disorder, panic disorder, social anxiety
486 disorder, or PMDD treated with PAXIL CR in controlled clinical studies, there were no reports
487 of mania or hypomania. As with all drugs effective in the treatment of major depressive disorder,
488 PAXIL CR should be used cautiously in patients with a history of mania.

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

496 **Discontinuation of Treatment With PAXIL CR:** Adverse events while discontinuing
497 therapy with PAXIL CR were not systematically evaluated in most clinical trials; however, in
498 recent placebo-controlled clinical trials utilizing daily doses of PAXIL CR up to 37.5 mg/day,
499 spontaneously reported adverse events while discontinuing therapy with PAXIL CR were
500 evaluated. Patients receiving 37.5 mg/day underwent an incremental decrease in the daily dose
501 by 12.5 mg/day to a dose of 25 mg/day for 1 week before treatment was stopped. For patients

502 receiving 25 mg/day or 12.5 mg/day, treatment was stopped without an incremental decrease in
503 dose. With this regimen in those studies, the following adverse events were reported for
504 PAXIL CR, at an incidence of 2% or greater for PAXIL CR and were at least twice that reported
505 for placebo: Dizziness, nausea, nervousness, and additional symptoms described by the
506 investigator as associated with tapering or discontinuing PAXIL CR (e.g., emotional lability,
507 headache, agitation, electric shock sensations, fatigue, and sleep disturbances). These events
508 were reported as serious in 0.3% of patients who discontinued therapy with PAXIL CR.

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

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

521 See also PRECAUTIONS—Pediatric Use, for adverse events reported upon discontinuation
522 of treatment with paroxetine in pediatric patients.

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

527 **Hyponatremia:** Hyponatremia may occur as a result of treatment with SSRIs and SNRIs,
528 including PAXIL CR. In many cases, this hyponatremia appears to be the result of the syndrome
529 of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than
530 110 mmol/L have been reported. Elderly patients may be at greater risk of developing
531 hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise
532 volume depleted may be at greater risk (see Geriatric Use). Discontinuation of PAXIL CR
533 should be considered in patients with symptomatic hyponatremia and appropriate medical
534 intervention should be instituted.

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

539 **Abnormal Bleeding:** SSRIs and SNRIs, including paroxetine, may increase the risk of
540 bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and
541 other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control

542 and cohort design) have demonstrated an association between use of drugs that interfere with
543 serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to
544 SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to
545 life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated
546 with the concomitant use of paroxetine and NSAIDs, aspirin, or other drugs that affect
547 coagulation.

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

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

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

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

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

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

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

581 Patients should be advised of the following issues and asked to alert their prescriber if these

582 occur while taking PAXIL CR.

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

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

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

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

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

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

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

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

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

619 **Drug Interactions: Tryptophan:** As with other serotonin reuptake inhibitors, an interaction
620 between paroxetine and tryptophan may occur when they are coadministered. Adverse
621 experiences, consisting primarily of headache, nausea, sweating, and dizziness, have been

622 reported when tryptophan was administered to patients taking immediate-release paroxetine.
623 Consequently, concomitant use of PAXIL CR with tryptophan is not recommended (see
624 WARNINGS—Serotonin Syndrome).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

741 **Lithium:** A multiple-dose study with immediate-release paroxetine hydrochloride has shown

742 that there is no pharmacokinetic interaction between paroxetine and lithium carbonate. However,
743 due to the potential for serotonin syndrome, caution is advised when immediate-release
744 paroxetine hydrochloride is coadministered with lithium.

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

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

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

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

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

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

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

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

779 **Mutagenesis:** Paroxetine produced no genotoxic effects in a battery of 5 in vitro and 2 in
780 vivo assays that included the following: Bacterial mutation assay, mouse lymphoma mutation
781 assay, unscheduled DNA synthesis assay, and tests for cytogenetic aberrations in vivo in mouse

782 bone marrow and in vitro in human lymphocytes and in a dominant lethal test in rats.

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

790 **Pregnancy:** Pregnancy Category D. See WARNINGS—Usage in Pregnancy: *Teratogenic and*
791 *Nonteratogenic Effects.*

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

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

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

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

806 Events reported upon discontinuation of treatment with immediate-release paroxetine
807 hydrochloride in the pediatric clinical trials that included a taper phase regimen, which occurred
808 in at least 2% of patients who received immediate-release paroxetine hydrochloride and which
809 occurred at a rate at least twice that of placebo, were: emotional lability (including suicidal
810 ideation, suicide attempt, mood changes, and tearfulness), nervousness, dizziness, nausea, and
811 abdominal pain (see Discontinuation of Treatment With PAXIL CR).

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

815 In worldwide premarketing clinical trials with immediate-release paroxetine hydrochloride,
816 17% of paroxetine-treated patients (approximately 700) were 65 years or older. Pharmacokinetic
817 studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended;
818 there were, however, no overall differences in the adverse event profile between elderly and
819 younger patients, and effectiveness was similar in younger and older patients (see CLINICAL
820 PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

821 In a controlled study focusing specifically on elderly patients with major depressive disorder,

822 PAXIL CR was demonstrated to be safe and effective in the treatment of elderly patients (>60
823 years) with major depressive disorder. (See CLINICAL PHARMACOLOGY—Clinical Trials
824 and ADVERSE REACTIONS—Table 2.)

825 **ADVERSE REACTIONS**

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

837 **Adverse Findings Observed in Short-Term, Placebo-Controlled Trials With PAXIL** 838 **CR:**

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

845
846 In a placebo-controlled study of elderly patients with major depressive disorder, 13% (13/104)
847 of patients treated with PAXIL CR discontinued due to an adverse event. Events meeting the
848 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%

849

850 **Panic Disorder:** Eleven percent (50/444) of patients treated with PAXIL CR in panic
851 disorder studies discontinued treatment due to an adverse event. Events meeting the above
852 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%

853

854 **Social Anxiety Disorder:** Three percent (5/186) of patients treated with PAXIL CR in the
855 social anxiety disorder study discontinued treatment due to an adverse event. Events meeting the
856 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%

857

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

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

868 (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*	6.0%	2.4%	0.9%
Asthenia	4.9%	3.0%	1.4%
Somnolence*	4.3%	1.8%	0.3%
Insomnia	2.3%	1.5%	0.0%
Concentration Impaired*	2.0%	0.6%	0.3%
Dry mouth*	2.0%	0.6%	0.3%
Dizziness*	1.7%	0.6%	0.6%
Decreased Appetite*	1.4%	0.6%	0.0%
Sweating*	1.4%	0.0%	0.3%
Tremor*	1.4%	0.3%	0.0%
Yawn*	1.1%	0.0%	0.0%
Diarrhea	0.9%	1.2%	0.0%

869 * Events considered to be dose dependent are defined as events having an incidence rate with
 870 25 mg of PAXIL CR that was at least twice that with 12.5 mg of PAXIL CR (as well as the
 871 placebo group).

872

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

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

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

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

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

893 In the luteal phase dosing PMDD trial, which employed dosing of 12.5 mg/day or 25 mg/day
894 of PAXIL CR limited to the 2 weeks prior to the onset of menses over 3 consecutive menstrual
895 cycles, adverse events were evaluated during the first 14 days of each off-drug phase. When the
896 3 off-drug phases were combined, the following adverse events were reported at an incidence of
897 2% or greater for PAXIL CR and were at least twice the rate of that reported for placebo:
898 Infection (5.3% versus 2.5%), depression (2.8% versus 0.8%), insomnia (2.4% versus 0.8%),
899 sinusitis (2.4% versus 0%), and asthenia (2.0% versus 0.8%).

900 **Incidence in Controlled Clinical Trials:** Table 2 enumerates adverse events that occurred at
901 an incidence of 1% or more among patients treated with PAXIL CR, aged 18 to 65, who
902 participated in 2 short-term (12-week) placebo-controlled trials in major depressive disorder in
903 which patients were dosed in a range of 25 mg to 62.5 mg/day. Table 3 enumerates adverse
904 events reported at an incidence of 5% or greater among elderly patients (ages 60 to 88) treated
905 with PAXIL CR who participated in a short-term (12-week) placebo-controlled trial in major
906 depressive disorder in which patients were dosed in a range of 12.5 mg to 50 mg/day. Table 4
907 enumerates adverse events reported at an incidence of 1% or greater among patients (19 to 72
908 years) treated with PAXIL CR who participated in short-term (10-week) placebo-controlled trials
909 in panic disorder in which patients were dosed in a range of 12.5 mg to 75 mg/day. Table 5
910 enumerates adverse events reported at an incidence of 1% or greater among adult patients treated
911 with PAXIL CR who participated in a short-term (12-week), double-blind, placebo-controlled
912 trial in social anxiety disorder in which patients were dosed in a range of 12.5 to 37.5 mg/day.
913 Table 6 enumerates adverse events that occurred at an incidence of 1% or more among patients
914 treated with PAXIL CR who participated in three, 12-week, placebo-controlled trials in PMDD
915 in which patients were dosed at 12.5 mg/day or 25 mg/day and in one 12-week
916 placebo-controlled trial in which patients were dosed for 2 weeks prior to the onset of menses
917 (luteal phase dosing) at 12.5 mg/day or 25 mg/day. Reported adverse events were classified
918 using a standard COSTART-based Dictionary terminology.

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

926

927 **Table 2. Treatment-Emergent Adverse Events Occurring in $\geq 1\%$ of Patients**928 **Treated With PAXIL CR in a Pool of 2 Studies in Major Depressive**929 **Disorder^{1,2}**

Body System/Adverse Event	% Reporting Event	
	PAXIL CR (n = 212)	Placebo (n = 211)
Body as a Whole		
Headache	27%	20%
Asthenia	14%	9%
Infection ³	8%	5%
Abdominal Pain	7%	4%
Back Pain	5%	3%
Trauma ⁴	5%	1%
Pain ⁵	3%	1%
Allergic Reaction ⁶	2%	1%
Cardiovascular System		
Tachycardia	1%	0%
Vasodilatation ⁷	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 ⁸	5%	1%
Taste Perversion	2%	0%
Urogenital System		
Abnormal Ejaculation ^{9,10}	26%	1%
Female Genital Disorder ^{9,11}	10%	<1%
Impotence ⁹	5%	3%
Urinary Tract Infection	3%	1%
Menstrual Disorder ⁹	2%	<1%
Vaginitis ⁹	2%	0%

- 931 1. Adverse events for which the PAXIL CR reporting incidence was less than or
932 equal to the placebo incidence are not included. These events are: Abnormal
933 dreams, anxiety, arthralgia, depersonalization, dysmenorrhea, dyspepsia,
934 hyperkinesia, increased appetite, myalgia, nervousness, pharyngitis, purpura,
935 rash, respiratory disorder, sinusitis, urinary frequency, and weight gain.
- 936 2. <1% means greater than zero and less than 1%.
- 937 3. Mostly flu.
- 938 4. A wide variety of injuries with no obvious pattern.
- 939 5. Pain in a variety of locations with no obvious pattern.
- 940 6. Most frequently seasonal allergic symptoms.
- 941 7. Usually flushing.
- 942 8. Mostly blurred vision.
- 943 9. Based on the number of males or females.
- 944 10. Mostly anorgasmia or delayed ejaculation.
- 945 11. Mostly anorgasmia or delayed orgasm.

946

947 **Table 3. Treatment-Emergent Adverse Events Occurring in $\geq 5\%$ of**
948 **Patients Treated With PAXIL CR in a Study of Elderly Patients With Major**
949 **Depressive Disorder^{1,2}**

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 ^{3,4}	17%	3%
Impotence ³	9%	3%

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

954 2. <1% means greater than zero and less than 1%.

955 3. Based on the number of males.

956 4. Mostly anorgasmia or delayed ejaculation.

957

958 **Table 4. Treatment-Emergent Adverse Events Occurring in $\geq 1\%$ of Patients**
959 **Treated With PAXIL CR in a Pool of 3 Panic Disorder Studies^{1,2}**

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 ³	5%	4%
Cardiovascular System		
Vasodilation ⁴	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 ⁵	2%	<1%
Myoclonus	2%	<1%
Respiratory System		
Sinusitis	8%	5%
Yawn	3%	0%
Skin and Appendages		
Sweating	7%	2%
Special Senses		
Abnormal Vision ⁶	3%	<1%
Urogenital System		
Abnormal Ejaculation ^{7,8}	27%	3%
Impotence ⁷	10%	1%
Female Genital Disorders ^{9,10}	7%	1%
Urinary Frequency	2%	<1%
Urination Impaired	2%	<1%
Vaginitis ⁹	1%	<1%

- 961 1. Adverse events for which the reporting rate for PAXIL CR was less than or equal to the
962 placebo rate are not included. These events are: Abnormal dreams, allergic reaction, back
963 pain, bronchitis, chest pain, concentration impaired, confusion, cough increased, depression,
964 dizziness, dysmenorrhea, dyspepsia, fever, flatulence, headache, increased appetite, infection,
965 menstrual disorder, migraine, pain, paresthesia, pharyngitis, respiratory disorder, rhinitis,
966 tachycardia, taste perversion, thinking abnormal, urinary tract infection, and vomiting.
- 967 2. <1% means greater than zero and less than 1%.
- 968 3. Various physical injuries.
- 969 4. Mostly flushing.
- 970 5. Mostly muscle tightness or stiffness.
- 971 6. Mostly blurred vision.
- 972 7. Based on the number of male patients.
- 973 8. Mostly anorgasmia or delayed ejaculation.
- 974 9. Based on the number of female patients.

975 10. Mostly anorgasmia or difficulty achieving orgasm.

976

977 **Table 5. Treatment-Emergent Adverse Effects Occurring in $\geq 1\%$ of Patients**
 978 **Treated With PAXIL CR in a Social Anxiety Disorder Study^{1,2}**

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 ³	3%	<1%
Allergic Reaction ⁴	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 ⁵	2%	0%
Abnormality of Accommodation	2%	0%
Urogenital System		
Abnormal Ejaculation ^{6,7}	15%	1%
Impotence ⁶	9%	0%
Female Genital Disorders ^{8,9}	3%	0%

- 979 1. Adverse events for which the reporting rate for PAXIL CR was less than or equal
980 to the placebo rate are not included. These events are: Dysmenorrhea, flatulence,
981 gastroenteritis, hypertonia, infection, pain, pharyngitis, rash, respiratory disorder,
982 rhinitis, and vomiting.
- 983 2. <1% means greater than zero and less than 1%.
- 984 3. Various physical injuries.
- 985 4. Most frequently seasonal allergic symptoms.
- 986 5. Mostly blurred vision.
- 987 6. Based on the number of male patients.
- 988 7. Mostly anorgasmia or delayed ejaculation.
- 989 8. Based on the number of female patients.
- 990 9. Mostly anorgasmia or difficulty achieving orgasm.
- 991

992 **Table 6. Treatment-Emergent Adverse Events Occurring in ≥1% of Patients Treated**
 993 **With PAXIL CR in a Pool of 3 Premenstrual Dysphoric Disorder Studies with**
 994 **Continuous Dosing or in 1 Premenstrual Dysphoric Disorder Study with Luteal Phase**
 995 **Dosing^{1,2,3}**

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 ⁴	8%	1%	2%	0%
Menorrhagia	1%	<1%	-	-
Vaginal Moniliasis	1%	<1%	-	-
Menstrual Disorder	-	-	1%	0%

- 996 1. Adverse events for which the reporting rate of PAXIL CR was less than or equal to the
997 placebo rate are not included. These events for continuous dosing are: Abdominal pain, back
998 pain, pain, trauma, weight gain, myalgia, pharyngitis, respiratory disorder, rhinitis, sinusitis,
999 pruritis, dysmenorrhea, menstrual disorder, urinary tract infection, and vomiting. The events
1000 for luteal phase dosing are: Allergic reaction, back pain, headache, infection, pain, trauma,
1001 myalgia, anxiety, pharyngitis, respiratory disorder, cystitis, and dysmenorrhea.
- 1002 2. <1% means greater than zero and less than 1%.
- 1003 3. The luteal phase and continuous dosing PMDD trials were not designed for making direct
1004 comparisons between the 2 dosing regimens. Therefore, a comparison between the 2 dosing
1005 regimens of the PMDD trials of incidence rates shown in Table 5 should be avoided.
- 1006 4. Mostly anorgasmia or difficulty achieving orgasm.

1007

1008 **Dose Dependency of Adverse Events:** The following table shows results in PMDD
1009 trials of common adverse events, defined as events with an incidence of $\geq 1\%$ with 25 mg of
1010 PAXIL CR that was at least twice that with 12.5 mg of PAXIL CR and with placebo.
1011

Incidence of Common Adverse Events in Placebo, 12.5 mg and 25 mg of PAXIL CR in a Pool of 3 Fixed-Dose PMDD Trials

Common Adverse Event	PAXIL CR 25 mg (n = 348)	PAXIL CR 12.5 mg (n = 333)	Placebo (n = 349)
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%

1012

1013 A comparison of adverse event rates in a fixed-dose study comparing immediate-release
1014 paroxetine with placebo in the treatment of major depressive disorder revealed a clear dose
1015 dependency for some of the more common adverse events associated with the use of
1016 immediate-release paroxetine.

1017 **Male and Female Sexual Dysfunction With SSRIs:** Although changes in sexual desire,
1018 sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric
1019 disorder, they may also be a consequence of pharmacologic treatment. In particular, some
1020 evidence suggests that SSRIs can cause such untoward sexual experiences.

1021 Reliable estimates of the incidence and severity of untoward experiences involving sexual
1022 desire, performance, and satisfaction are difficult to obtain; however, in part because patients and
1023 physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of
1024 untoward sexual experience and performance cited in product labeling, are likely to
1025 underestimate their actual incidence.

1026 The percentage of patients reporting symptoms of sexual dysfunction in the pool of 2
1027 placebo-controlled trials in nonelderly patients with major depressive disorder, in the pool of 3
1028 placebo-controlled trials in patients with panic disorder, in the placebo-controlled trial in patients
1029 with social anxiety disorder, and in the intermittent dosing and the pool of 3 placebo-controlled
1030 continuous dosing trials in female patients with PMDD are as follows:

1031

	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%

1032

1033 There are no adequate, controlled studies examining sexual dysfunction with paroxetine
1034 treatment.

1035 Paroxetine treatment has been associated with several cases of priapism. In those cases with a
1036 known outcome, patients recovered without sequelae.

1037 While it is difficult to know the precise risk of sexual dysfunction associated with the use of
1038 SSRIs, physicians should routinely inquire about such possible side effects.

1039 **Weight and Vital Sign Changes:** Significant weight loss may be an undesirable result of
1040 treatment with paroxetine for some patients but, on average, patients in controlled trials with
1041 PAXIL CR or the immediate-release formulation, had minimal weight loss (about 1 pound). No
1042 significant changes in vital signs (systolic and diastolic blood pressure, pulse, and temperature)
1043 were observed in patients treated with PAXIL CR, or immediate-release paroxetine
1044 hydrochloride, in controlled clinical trials.

1045 **ECG Changes:** In an analysis of ECGs obtained in 682 patients treated with
1046 immediate-release paroxetine and 415 patients treated with placebo in controlled clinical trials,
1047 no clinically significant changes were seen in the ECGs of either group.

1048 **Liver Function Tests:** In a pool of 2 placebo-controlled clinical trials, patients treated with
1049 PAXIL CR or placebo exhibited abnormal values on liver function tests at comparable rates. In
1050 particular, the controlled-release paroxetine-versus-placebo comparisons for alkaline
1051 phosphatase, SGOT, SGPT, and bilirubin revealed no differences in the percentage of patients
1052 with marked abnormalities.

1053 In a study of elderly patients with major depressive disorder, 3 of 104 patients treated with
1054 PAXIL CR and none of 109 placebo patients experienced liver transaminase elevations of
1055 potential clinical concern.

1056 Two of the patients treated with PAXIL CR dropped out of the study due to abnormal liver
1057 function tests; the third patient experienced normalization of transaminase levels with continued
1058 treatment. Also, in the pool of 3 studies of patients with panic disorder, 4 of 444 patients treated
1059 with PAXIL CR and none of 445 placebo patients experienced liver transaminase elevations of
1060 potential clinical concern. Elevations in all 4 patients decreased substantially after
1061 discontinuation of PAXIL CR. The clinical significance of these findings is unknown.

1062 In placebo-controlled clinical trials with the immediate-release formulation of paroxetine,
1063 patients exhibited abnormal values on liver function tests at no greater rate than that seen in
1064 placebo-treated patients.

1065 **Hallucinations:** In pooled clinical trials of immediate-release paroxetine hydrochloride,
1066 hallucinations were observed in 22 of 9,089 patients receiving drug and in 4 of 3,187 patients
1067 receiving placebo.

1068 **Other Events Observed During the Clinical Development of Paroxetine:** The
1069 following adverse events were reported during the clinical development of PAXIL CR and/or the
1070 clinical development of the immediate-release formulation of paroxetine.

1071 Adverse events for which frequencies are provided below occurred in clinical trials with the
1072 controlled-release formulation of paroxetine. During its premarketing assessment in major
1073 depressive disorder, panic disorder, social anxiety disorder, and PMDD, multiple doses of
1074 PAXIL CR were administered to 1,627 patients in phase 3 double-blind, controlled, outpatient
1075 studies. Untoward events associated with this exposure were recorded by clinical investigators
1076 using terminology of their own choosing. Consequently, it is not possible to provide a
1077 meaningful estimate of the proportion of individuals experiencing adverse events without first
1078 grouping similar types of untoward events into a smaller number of standardized event
1079 categories.

1080 In the tabulations that follow, reported adverse events were classified using a
1081 COSTART-based dictionary. The frequencies presented, therefore, represent the proportion of
1082 the 1,627 patients exposed to PAXIL CR who experienced an event of the type cited on at least 1
1083 occasion while receiving PAXIL CR. All reported events are included except those already listed
1084 in Tables 2 through 6 and those events where a drug cause was remote. If the COSTART term
1085 for an event was so general as to be uninformative, it was deleted or, when possible, replaced
1086 with a more informative term. It is important to emphasize that although the events reported
1087 occurred during treatment with paroxetine, they were not necessarily caused by it.

1088 Events are further categorized by body system and listed in order of decreasing frequency
1089 according to the following definitions: Frequent adverse events are those occurring on 1 or more
1090 occasions in at least 1/100 patients (only those not already listed in the tabulated results from
1091 placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in
1092 1/100 to 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients.

1093 Adverse events for which frequencies are not provided occurred during the premarketing
1094 assessment of immediate-release paroxetine in phase 2 and 3 studies of major depressive
1095 disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized

1096 anxiety disorder, and posttraumatic stress disorder. The conditions and duration of exposure to
1097 immediate-release paroxetine varied greatly and included (in overlapping categories) open and
1098 double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and
1099 fixed-dose and titration studies. Only those events not previously listed for controlled-release
1100 paroxetine are included. The extent to which these events may be associated with PAXIL CR is
1101 unknown.

1102 Events are listed alphabetically within the respective body system. Events of major clinical
1103 importance are also described in the PRECAUTIONS section.

1104 **Body as a Whole:** Infrequent were chills, face edema, fever, flu syndrome, malaise; rare
1105 were abscess, anaphylactoid reaction, anticholinergic syndrome, hypothermia; also observed
1106 were adrenergic syndrome, neck rigidity, sepsis.

1107 **Cardiovascular System:** Infrequent were angina pectoris, bradycardia, hematoma,
1108 hypertension, hypotension, palpitation, postural hypotension, supraventricular tachycardia,
1109 syncope; rare were bundle branch block; also observed were arrhythmia nodal, atrial fibrillation,
1110 cerebrovascular accident, congestive heart failure, low cardiac output, myocardial infarct,
1111 myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles,
1112 thrombophlebitis, thrombosis, vascular headache, ventricular extrasystoles.

1113 **Digestive System:** Infrequent were bruxism, dysphagia, eructation, gastritis,
1114 gastroenteritis, gastroesophageal reflux, gingivitis, hemorrhoids, liver function test abnormal,
1115 melena, pancreatitis, rectal hemorrhage, toothache, ulcerative stomatitis; rare were colitis,
1116 glossitis, gum hyperplasia, hepatosplenomegaly, increased salivation, intestinal obstruction,
1117 peptic ulcer, stomach ulcer, throat tightness; also observed were aphthous stomatitis, bloody
1118 diarrhea, bulimia, cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions,
1119 fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, jaundice, mouth
1120 ulceration, salivary gland enlargement, sialadenitis, stomatitis, tongue discoloration, tongue
1121 edema.

1122 **Endocrine System:** Infrequent were ovarian cyst, testes pain; rare were diabetes mellitus,
1123 hyperthyroidism; also observed were goiter, hypothyroidism, thyroiditis.

1124 **Hemic and Lymphatic System:** Infrequent were anemia, eosinophilia, hypochromic
1125 anemia, leukocytosis, leukopenia, lymphadenopathy, purpura; rare were thrombocytopenia; also
1126 observed were anisocytosis, basophilia, bleeding time increased, lymphedema, lymphocytosis,
1127 lymphopenia, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia.

1128 **Metabolic and Nutritional Disorders:** Infrequent were generalized edema,
1129 hyperglycemia, hypokalemia, peripheral edema, SGOT increased, SGPT increased, thirst; rare
1130 were bilirubinemia, dehydration, hyperkalemia, obesity; also observed were alkaline phosphatase
1131 increased, BUN increased, creatinine phosphokinase increased, gamma globulins increased,
1132 gout, hypercalcemia, hypercholesteremia, hyperphosphatemia, hypocalcemia, hypoglycemia,
1133 hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased.

1134 **Musculoskeletal System:** Infrequent were arthritis, bursitis, tendonitis; rare were
1135 myasthenia, myopathy, myositis; also observed were generalized spasm, osteoporosis,

1136 tenosynovitis, tetany.

1137 **Nervous System:** Frequent were depression; infrequent were amnesia, convulsion,
1138 depersonalization, dystonia, emotional lability, hallucinations, hyperkinesia, hypesthesia,
1139 hypokinesia, incoordination, libido increased, neuralgia, neuropathy, nystagmus, paralysis,
1140 vertigo; rare were ataxia, coma, diplopia, dyskinesia, hostility, paranoid reaction, torticollis,
1141 withdrawal syndrome; also observed were abnormal gait, akathisia, akinesia, aphasia,
1142 choreoathetosis, circumoral paresthesia, delirium, delusions, dysarthria, euphoria, extrapyramidal
1143 syndrome, fasciculations, grand mal convulsion, hyperalgesia, irritability, manic reaction,
1144 manic-depressive reaction, meningitis, myelitis, peripheral neuritis, psychosis, psychotic
1145 depression, reflexes decreased, reflexes increased, stupor, trismus.

1146 **Respiratory System:** Frequent were pharyngitis; infrequent were asthma, dyspnea,
1147 epistaxis, laryngitis, pneumonia; rare were stridor; also observed were dysphonia, emphysema,
1148 hemoptysis, hiccups, hyperventilation, lung fibrosis, pulmonary edema, respiratory flu, sputum
1149 increased.

1150 **Skin and Appendages:** Frequent were rash; infrequent were acne, alopecia, dry skin,
1151 eczema, pruritus, urticaria; rare were exfoliative dermatitis, furunculosis, pustular rash,
1152 seborrhea; also observed were angioedema, ecchymosis, erythema multiforme, erythema
1153 nodosum, hirsutism, maculopapular rash, skin discoloration, skin hypertrophy, skin ulcer,
1154 sweating decreased, vesiculobullous rash.

1155 **Special Senses:** Infrequent were conjunctivitis, earache, keratoconjunctivitis, mydriasis,
1156 photophobia, retinal hemorrhage, tinnitus; rare were blepharitis, visual field defect; also observed
1157 were amblyopia, anisocoria, blurred vision, cataract, conjunctival edema, corneal ulcer, deafness,
1158 exophthalmos, glaucoma, hyperacusis, night blindness, parosmia, ptosis, taste loss.

1159 **Urogenital System:** Frequent were dysmenorrhea^{*}; infrequent were albuminuria,
1160 amenorrhea^{*}, breast pain^{*}, cystitis, dysuria, prostatitis^{*}, urinary retention; rare were breast
1161 enlargement^{*}, breast neoplasm^{*}, female lactation, hematuria, kidney calculus, metrorrhagia^{*},
1162 nephritis, nocturia, pregnancy and puerperal disorders^{*}, salpingitis, urinary incontinence, uterine
1163 fibroids enlarged^{*}; also observed were breast atrophy, ejaculatory disturbance, endometrial
1164 disorder, epididymitis, fibrocystic breast, leukorrhea, mastitis, oliguria, polyuria, pyuria,
1165 urethritis, urinary casts, urinary urgency, urolith, uterine spasm, vaginal hemorrhage.

1166 ^{*}Based on the number of men and women as appropriate.

1167 **Postmarketing Reports:** Voluntary reports of adverse events in patients taking
1168 immediate-release paroxetine hydrochloride that have been received since market introduction
1169 and not listed above that may have no causal relationship with the drug include acute
1170 pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis,
1171 and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré
1172 syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion,
1173 symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome-like
1174 events, serotonin syndrome; extrapyramidal symptoms which have included akathisia,
1175 bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been

1176 associated with concomitant use of pimozone; tremor and trismus; status epilepticus, acute renal
1177 failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic
1178 neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including torsade de pointes),
1179 thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including
1180 aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic
1181 syndromes (such as Henoch-Schönlein purpura). There has been a case report of an elevated
1182 phenytoin level after 4 weeks of immediate-release paroxetine and phenytoin coadministration.
1183 There has been a case report of severe hypotension when immediate-release paroxetine was
1184 added to chronic metoprolol treatment.

1185 **DRUG ABUSE AND DEPENDENCE**

1186 **Controlled Substance Class:** PAXIL CR is not a controlled substance.

1187 **Physical and Psychologic Dependence:** PAXIL CR has not been systematically studied
1188 in animals or humans for its potential for abuse, tolerance or physical dependence. While the
1189 clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were
1190 not systematic and it is not possible to predict on the basis of this limited experience the extent to
1191 which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently,
1192 patients should be evaluated carefully for history of drug abuse, and such patients should be
1193 observed closely for signs of misuse or abuse of PAXIL CR (e.g., development of tolerance,
1194 incrementations of dose, drug-seeking behavior).

1195 **OVERDOSAGE**

1196 **Human Experience:** Since the introduction of immediate-release paroxetine hydrochloride in
1197 the United States, 342 spontaneous cases of deliberate or accidental overdose during
1198 paroxetine treatment have been reported worldwide (circa 1999). These include overdoses with
1199 paroxetine alone and in combination with other substances. Of these, 48 cases were fatal and of
1200 the fatalities, 17 appeared to involve paroxetine alone. Eight fatal cases that documented the
1201 amount of paroxetine ingested were generally confounded by the ingestion of other drugs or
1202 alcohol or the presence of significant comorbid conditions. Of 145 non-fatal cases with known
1203 outcome, most recovered without sequelae. The largest known ingestion involved 2,000 mg of
1204 paroxetine (33 times the maximum recommended daily dose) in a patient who recovered.

1205 Commonly reported adverse events associated with paroxetine overdose include
1206 somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other
1207 notable signs and symptoms observed with overdoses involving paroxetine (alone or with other
1208 substances) include mydriasis, convulsions (including status epilepticus), ventricular
1209 dysrhythmias (including torsade de pointes), hypertension, aggressive reactions, syncope,
1210 hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction
1211 (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin
1212 syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

1213 **Overdosage Management:** Treatment should consist of those general measures employed in
1214 the management of overdose with any drugs effective in the treatment of major depressive

1215 disorder.

1216 Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital
1217 signs. General supportive and symptomatic measures are also recommended. Induction of emesis
1218 is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway
1219 protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic
1220 patients.

1221 Activated charcoal should be administered. Due to the large volume of distribution of this
1222 drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of
1223 benefit. No specific antidotes for paroxetine are known.

1224 A specific caution involves patients taking or recently having taken paroxetine who might
1225 ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the
1226 parent tricyclic and an active metabolite may increase the possibility of clinically significant
1227 sequelae and extend the time needed for close medical observation (see PRECAUTIONS—
1228 *Drugs Metabolized by Cytochrome CYP2D6*).

1229 In managing overdose, consider the possibility of multiple-drug involvement. The physician
1230 should consider contacting a poison control center for additional information on the treatment of
1231 any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians'*
1232 *Desk Reference* (PDR).

1233 **DOSAGE AND ADMINISTRATION**

1234 **Major Depressive Disorder: Usual Initial Dosage:** PAXIL CR should be administered as
1235 a single daily dose, usually in the morning, with or without food. The recommended initial dose
1236 is 25 mg/day. Patients were dosed in a range of 25 mg to 62.5 mg/day in the clinical trials
1237 demonstrating the effectiveness of PAXIL CR in the treatment of major depressive disorder. As
1238 with all drugs effective in the treatment of major depressive disorder, the full effect may be
1239 delayed. Some patients not responding to a 25-mg dose may benefit from dose increases, in
1240 12.5-mg/day increments, up to a maximum of 62.5 mg/day. Dose changes should occur at
1241 intervals of at least 1 week.

1242 Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be
1243 swallowed whole.

1244 **Maintenance Therapy:** There is no body of evidence available to answer the question of
1245 how long the patient treated with PAXIL CR should remain on it. It is generally agreed that acute
1246 episodes of major depressive disorder require several months or longer of sustained
1247 pharmacologic therapy. Whether the dose of an antidepressant needed to induce remission is
1248 identical to the dose needed to maintain and/or sustain euthymia is unknown.

1249 Systematic evaluation of the efficacy of immediate-release paroxetine hydrochloride has
1250 shown that efficacy is maintained for periods of up to 1 year with doses that averaged about
1251 30 mg, which corresponds to a 37.5-mg dose of PAXIL CR, based on relative bioavailability
1252 considerations (see CLINICAL PHARMACOLOGY—Pharmacokinetics).

1253 **Panic Disorder: Usual Initial Dosage:** PAXIL CR should be administered as a single daily
1254 dose, usually in the morning. Patients should be started on 12.5 mg/day. Dose changes should
1255 occur in 12.5-mg/day increments and at intervals of at least 1 week. Patients were dosed in a
1256 range of 12.5 to 75 mg/day in the clinical trials demonstrating the effectiveness of PAXIL CR.
1257 The maximum dosage should not exceed 75 mg/day.

1258 Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be
1259 swallowed whole.

1260 **Maintenance Therapy:** Long-term maintenance of efficacy with the immediate-release
1261 formulation of paroxetine was demonstrated in a 3-month relapse prevention trial. In this trial,
1262 patients with panic disorder assigned to immediate-release paroxetine demonstrated a lower
1263 relapse rate compared to patients on placebo. Panic disorder is a chronic condition, and it is
1264 reasonable to consider continuation for a responding patient. Dosage adjustments should be
1265 made to maintain the patient on the lowest effective dosage, and patients should be periodically
1266 reassessed to determine the need for continued treatment.

1267 **Social Anxiety Disorder: Usual Initial Dosage:** PAXIL CR should be administered as a
1268 single daily dose, usually in the morning, with or without food. The recommended initial dose is
1269 12.5 mg/day. Patients were dosed in a range of 12.5 mg to 37.5 mg/day in the clinical trial
1270 demonstrating the effectiveness of PAXIL CR in the treatment of social anxiety disorder. If the
1271 dose is increased, this should occur at intervals of at least 1 week, in increments of 12.5 mg/day,
1272 up to a maximum of 37.5 mg/day.

1273 Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be
1274 swallowed whole.

1275 **Maintenance Therapy:** There is no body of evidence available to answer the question of
1276 how long the patient treated with PAXIL CR should remain on it. Although the efficacy of
1277 PAXIL CR beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials,
1278 social anxiety disorder is recognized as a chronic condition, and it is reasonable to consider
1279 continuation of treatment for a responding patient. Dosage adjustments should be made to
1280 maintain the patient on the lowest effective dosage, and patients should be periodically
1281 reassessed to determine the need for continued treatment.

1282 **Premenstrual Dysphoric Disorder: Usual Initial Dosage:** PAXIL CR should be
1283 administered as a single daily dose, usually in the morning, with or without food. PAXIL CR
1284 may be administered either daily throughout the menstrual cycle or limited to the luteal phase of
1285 the menstrual cycle, depending on physician assessment. The recommended initial dose is
1286 12.5 mg/day. In clinical trials, both 12.5 mg/day and 25 mg/day were shown to be effective.
1287 Dose changes should occur at intervals of at least 1 week.

1288 Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be
1289 swallowed whole.

1290 **Maintenance/Continuation Therapy:** The effectiveness of PAXIL CR for a period
1291 exceeding 3 menstrual cycles has not been systematically evaluated in controlled trials.
1292 However, women commonly report that symptoms worsen with age until relieved by the onset of

1293 menopause. Therefore, it is reasonable to consider continuation of a responding patient. Patients
1294 should be periodically reassessed to determine the need for continued treatment.

1295 **Special Populations: Treatment of Pregnant Women During the Third Trimester:**

1296 Neonates exposed to PAXIL CR and other SSRIs or SNRIs, late in the third trimester have
1297 developed complications requiring prolonged hospitalization, respiratory support, and tube
1298 feeding (see WARNINGS). When treating pregnant women with paroxetine during the third
1299 trimester, the physician should carefully consider the potential risks and benefits of treatment.
1300 The physician may consider tapering paroxetine in the third trimester.

1301 **Dosage for Elderly or Debilitated Patients, and Patients With Severe Renal or**
1302 **Hepatic Impairment:** The recommended initial dose of PAXIL CR is 12.5 mg/day for elderly
1303 patients, debilitated patients, and/or patients with severe renal or hepatic impairment. Increases
1304 may be made if indicated. Dosage should not exceed 50 mg/day.

1305 **Switching Patients to or From a Monoamine Oxidase Inhibitor:** At least 14 days
1306 should elapse between discontinuation of an MAOI and initiation of therapy with PAXIL CR.
1307 Similarly, at least 14 days should be allowed after stopping PAXIL CR before starting an MAOI.

1308 **Discontinuation of Treatment With PAXIL CR:** Symptoms associated with discontinuation
1309 of immediate-release paroxetine hydrochloride or PAXIL CR have been reported (see
1310 PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing
1311 treatment, regardless of the indication for which PAXIL CR is being prescribed. A gradual
1312 reduction in the dose rather than abrupt cessation is recommended whenever possible. If
1313 intolerable symptoms occur following a decrease in the dose or upon discontinuation of
1314 treatment, then resuming the previously prescribed dose may be considered. Subsequently, the
1315 physician may continue decreasing the dose but at a more gradual rate.

1316 **HOW SUPPLIED**

1317 PAXIL CR is supplied as an enteric film-coated, controlled-release, round tablet, as follows:

1318 12.5-mg yellow tablets, engraved with PAXIL CR and 12.5

1319 NDC 0029-3206-13 Bottles of 30

1320 25-mg pink tablets, engraved with PAXIL CR and 25

1321 NDC 0029-3207-13 Bottles of 30

1322 37.5 mg blue tablets, engraved with PAXIL CR and 37.5

1323 NDC 0029-3208-13 Bottles of 30

1324 Store at or below 25°C (77°F) [see USP].

1325

1326 PAXIL CR is a registered trademark of GlaxoSmithKline.

1327 GEOMATRIX is a trademark of Jago Pharma, Muttenz, Switzerland.

1328
1329 **Medication Guide**

1330 **Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal**
1331 **Thoughts or Actions**

1332 **PAXIL CR[®] (PAX-il) (paroxetine hydrochloride) Controlled-Release Tablets**
1333

1334 Read the Medication Guide that comes with your or your family member's antidepressant
1335 medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with
1336 antidepressant medicines. **Talk to your, or your family member's, healthcare provider**
1337 **about:**

- 1338 • All risks and benefits of treatment with antidepressant medicines
- 1339 • All treatment choices for depression or other serious mental illness

1340
1341 **What is the most important information I should know about antidepressant medicines,**
1342 **depression and other serious mental illnesses, and suicidal thoughts or action?**
1343

- 1344 **1. Antidepressant medicines may increase suicidal thoughts or actions in some children,**
1345 **teenagers, and young adults within the first few months of treatment.**
1346
- 1347 **2. Depression and other serious mental illnesses are the most important causes of suicidal**
1348 **thoughts and actions. Some people may have a particularly high risk of having suicidal**
1349 **thoughts or actions.** These include people who have (or have a family history of) bipolar
1350 illness (also called manic-depressive illness) or suicidal thoughts or actions.
1351
- 1352 **3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a**
1353 **family member?**
1354
 - 1355 • Pay close attention to any changes, especially sudden changes, in mood, behaviors,
 - 1356 thoughts, or feelings. This is very important when an antidepressant medicine is started or
 - 1357 when the dose is changed.
 - 1358 • Call the healthcare provider right away to report new or sudden changes in mood,
 - 1359 behavior, thoughts, or feelings.
 - 1360 • Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare
 - 1361 provider between visits as needed, especially if you have concerns about symptoms.

1362
1363 **Call a healthcare provider right away if you or your family member has any of the**
1364 **following symptoms, especially if they are new, worse, or worry you:**
1365

- 1366 • Thoughts about suicide or dying
- 1367 • Attempts to commit suicide
- 1368 • New or worse depression

- 1369 • New or worse anxiety
- 1370 • Feeling very agitated or restless
- 1371 • Panic attacks
- 1372 • Trouble sleeping (insomnia)
- 1373 • New or worse irritability
- 1374 • Acting aggressive, being angry, or violent
- 1375 • Acting on dangerous impulses
- 1376 • An extreme increase in activity and talking (mania)
- 1377 • Other unusual changes in behavior or mood

1378

1379 **What else do I need to know about antidepressant medicines?**

1380

- 1381 • **Never stop an antidepressant medicine without first talking to a healthcare**
- 1382 **provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- 1383
- 1384 • **Antidepressants are medicines used to treat depression and other illnesses.** It is
- 1385 important to discuss all the risks of treating depression and also the risks of not treating it.
- 1386 Patients and their families or other caregivers should discuss all treatment choices with
- 1387 the healthcare provider, not just the use of antidepressants.
- 1388
- 1389 • **Antidepressant medicines have other side effects.** Call your doctor for medical advice
- 1390 about side effects. You may report side effects to FDA at 1-800-FDA-1088.
- 1391
- 1392 • **Antidepressant medicines can interact with other medicines.** Know all of the
- 1393 medicines that you or your family member takes. Keep a list of all medicines to show the
- 1394 healthcare provider. Do not start new medicines without first checking with your
- 1395 healthcare provider.
- 1396
- 1397 • **Not all antidepressant medicines prescribed for children are FDA approved for use**
- 1398 **in children.** Talk to your child's healthcare provider for more information.
- 1399

1400 This Medication Guide has been approved by the U.S. Food and Drug Administration for all
1401 antidepressants.

1402

1403 January 2008

PCR:3MG

1404



1405

1406 GlaxoSmithKline

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1408
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1411 Month Year

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