

1 PRESCRIBING INFORMATION

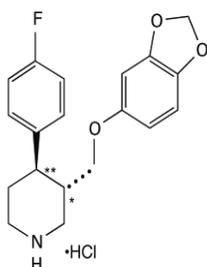
2 **PAXIL[®]**
3 **(paroxetine hydrochloride)**
4 **Tablets and Oral Suspension**
5

6 **Suicidality and Antidepressant Drugs**

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

21 **DESCRIPTION**

22 PAXIL (paroxetine hydrochloride) is an orally administered psychotropic drug. It is the
23 hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-*trans*-4*R*-(4'-
24 fluorophenyl)-3*S*-[(3',4'-methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate
25 and has the empirical formula of C₁₉H₂₀FNO₃•HCl•1/2H₂O. The molecular weight is 374.8
26 (329.4 as free base). The structural formula of paroxetine hydrochloride is:



27
28 Paroxetine hydrochloride is an odorless, off-white powder, having a melting point range of
29 120° to 138°C and a solubility of 5.4 mg/mL in water.

30 **Tablets:** Each film-coated tablet contains paroxetine hydrochloride equivalent to paroxetine as
31 follows: 10 mg–yellow (scored); 20 mg–pink (scored); 30 mg–blue, 40 mg–green. Inactive
32 ingredients consist of dibasic calcium phosphate dihydrate, hypromellose, magnesium stearate,
33 polyethylene glycols, polysorbate 80, sodium starch glycolate, titanium dioxide, and 1 or more of

34 the following: D&C Red No. 30 aluminum lake, D&C Yellow No. 10 aluminum lake, FD&C
35 Blue No. 2 aluminum lake, FD&C Yellow No. 6 aluminum lake.

36 **Suspension for Oral Administration:** Each 5 mL of orange-colored, orange-flavored liquid
37 contains paroxetine hydrochloride equivalent to paroxetine, 10 mg. Inactive ingredients consist
38 of polacrillin potassium, microcrystalline cellulose, propylene glycol, glycerin, sorbitol,
39 methylparaben, propylparaben, sodium citrate dihydrate, citric acid anhydrous, sodium
40 saccharin, flavorings, FD&C Yellow No. 6 aluminum lake, and simethicone emulsion, USP.

41 **CLINICAL PHARMACOLOGY**

42 **Pharmacodynamics:** The efficacy of paroxetine in the treatment of major depressive
43 disorder, social anxiety disorder, obsessive compulsive disorder (OCD), panic disorder (PD),
44 generalized anxiety disorder (GAD), and posttraumatic stress disorder (PTSD) is presumed to be
45 linked to potentiation of serotonergic activity in the central nervous system resulting from
46 inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT). Studies at clinically
47 relevant doses in humans have demonstrated that paroxetine blocks the uptake of serotonin into
48 human platelets. In vitro studies in animals also suggest that paroxetine is a potent and highly
49 selective inhibitor of neuronal serotonin reuptake and has only very weak effects on
50 norepinephrine and dopamine neuronal reuptake. In vitro radioligand binding studies indicate
51 that paroxetine has little affinity for muscarinic, α_1 -, α_2 -, beta-adrenergic-, dopamine
52 (D_2)-, 5-HT₁-, 5-HT₂-, and histamine (H_1)-receptors; antagonism of muscarinic, histaminergic,
53 and α_1 -adrenergic receptors has been associated with various anticholinergic, sedative, and
54 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 mean elimination half-life is approximately 21 hours
59 (CV 32%) after oral dosing of 30 mg tablets of PAXIL daily for 30 days. Paroxetine is
60 extensively metabolized and the metabolites are considered to be inactive. Nonlinearity in
61 pharmacokinetics is observed with increasing doses. Paroxetine metabolism is mediated in part
62 by CYP2D6, and the metabolites are primarily excreted in the urine and to some extent in the
63 feces. Pharmacokinetic behavior of paroxetine has not been evaluated in subjects who are
64 deficient in CYP2D6 (poor metabolizers).

65 [In a meta analysis of paroxetine from 4 studies done in healthy volunteers following
66 multiple dosing of 20 mg/day to 40 mg/day, males did not exhibit a significantly lower
67 C_{max} or AUC than females.](#)

68 **Absorption and Distribution:** Paroxetine is equally bioavailable from the oral suspension
69 and tablet.

70 Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the
71 hydrochloride salt. In a study in which normal male subjects (n = 15) received 30 mg tablets
72 daily for 30 days, steady-state paroxetine concentrations were achieved by approximately
73 10 days for most subjects, although it may take substantially longer in an occasional patient. At

74 steady state, mean values of C_{\max} , T_{\max} , C_{\min} , and $T_{1/2}$ were 61.7 ng/mL (CV 45%), 5.2 hr.
75 (CV 10%), 30.7 ng/mL (CV 67%), and 21.0 hours (CV 32%), respectively. The steady-state C_{\max}
76 and C_{\min} values were about 6 and 14 times what would be predicted from single-dose studies.
77 Steady-state drug exposure based on AUC_{0-24} was about 8 times greater than would have been
78 predicted from single-dose data in these subjects. The excess accumulation is a consequence of
79 the fact that 1 of the enzymes that metabolizes paroxetine is readily saturable.

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

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

86 Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/mL and
87 400 ng/mL, respectively. Under clinical conditions, paroxetine concentrations would normally be
88 less than 400 ng/mL. Paroxetine does not alter the in vitro protein binding of phenytoin or
89 warfarin.

90 **Metabolism and Excretion:** The mean elimination half-life is approximately 21 hours
91 (CV 32%) after oral dosing of 30 mg tablets daily for 30 days of PAXIL. In steady-state dose
92 proportionality studies involving elderly and nonelderly patients, at doses of 20 mg to 40 mg
93 daily for the elderly and 20 mg to 50 mg daily for the nonelderly, some nonlinearity was
94 observed in both populations, again reflecting a saturable metabolic pathway. In comparison to
95 C_{\min} values after 20 mg daily, values after 40 mg daily were only about 2 to 3 times greater than
96 doubled.

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

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

110 **Other Clinical Pharmacology Information: Specific Populations: Renal and Liver**
111 **Disease:** Increased plasma concentrations of paroxetine occur in subjects with renal and
112 hepatic impairment. The mean plasma concentrations in patients with creatinine clearance below
113 30 mL/min. were approximately 4 times greater than seen in normal volunteers. Patients with

114 creatinine clearance of 30 to 60 mL/min. and patients with hepatic functional impairment had
115 about a 2-fold increase in plasma concentrations (AUC, C_{max}).

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

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

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

127 **Clinical Trials**

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

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

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

153 approximately 7 points on the YBOCS total score, which was significantly greater than the mean
154 reduction of approximately 4 points in placebo-treated patients.

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

157

Outcome Classification (%) on CGI-Global Improvement Item for Completers in Study 1				
Outcome Classification	Placebo (n = 74)	PAXIL 20 mg (n = 75)	PAXIL 40 mg (n = 66)	PAXIL 60 mg (n = 66)
Worse	14%	7%	7%	3%
No Change	44%	35%	22%	19%
Minimally Improved	24%	33%	29%	34%
Much Improved	11%	18%	22%	24%
Very Much Improved	7%	7%	20%	20%

158

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

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

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

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

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

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

184 In both Studies 2 and 3, the mean paroxetine dose for completers at endpoint was

185 approximately 40 mg/day of paroxetine.

186 Long-term maintenance effects of PAXIL in panic disorder were demonstrated in an
187 extension to Study 1. Patients who were responders during the 10-week double-blind phase and
188 during a 3-month double-blind extension phase were randomized to either paroxetine (10, 20, or
189 40 mg/day) or placebo in a 3-month double-blind relapse prevention phase. Patients randomized
190 to paroxetine were significantly less likely to relapse than comparably treated patients who were
191 randomized to placebo.

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

194 **Social Anxiety Disorder:** The effectiveness of PAXIL in the treatment of social anxiety
195 disorder was demonstrated in three 12-week, multicenter, placebo-controlled studies (Studies 1,
196 2, and 3) of adult outpatients with social anxiety disorder (DSM-IV). In these studies, the
197 effectiveness of PAXIL compared to placebo was evaluated on the basis of (1) the proportion of
198 responders, as defined by a Clinical Global Impression (CGI) Improvement score of 1 (very
199 much improved) or 2 (much improved), and (2) change from baseline in the Liebowitz Social
200 Anxiety Scale (LSAS).

201 Studies 1 and 2 were flexible-dose studies comparing paroxetine (20 to 50 mg daily) and
202 placebo. Paroxetine demonstrated statistically significant superiority over placebo on both the
203 CGI Improvement responder criterion and the Liebowitz Social Anxiety Scale (LSAS). In
204 Study 1, for patients who completed to week 12, 69% of paroxetine-treated patients compared to
205 29% of placebo-treated patients were CGI Improvement responders. In Study 2, CGI
206 Improvement responders were 77% and 42% for the paroxetine- and placebo-treated patients,
207 respectively.

208 Study 3 was a 12-week study comparing fixed paroxetine doses of 20, 40, or 60 mg/day with
209 placebo. Paroxetine 20 mg was demonstrated to be significantly superior to placebo on both the
210 LSAS Total Score and the CGI Improvement responder criterion; there were trends for
211 superiority over placebo for the 40 mg and 60 mg/day dose groups. There was no indication in
212 this study of any additional benefit for doses higher than 20 mg/day.

213 Subgroup analyses generally did not indicate differences in treatment outcomes as a function
214 of age, race, or gender.

215 **Generalized Anxiety Disorder:** The effectiveness of PAXIL in the treatment of Generalized
216 Anxiety Disorder (GAD) was demonstrated in two 8-week, multicenter, placebo-controlled
217 studies (Studies 1 and 2) of adult outpatients with Generalized Anxiety Disorder (DSM-IV).

218 Study 1 was an 8-week study comparing fixed paroxetine doses of 20 mg or 40 mg/day with
219 placebo. Doses of 20 mg or 40 mg of PAXIL were both demonstrated to be significantly superior
220 to placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score. There was not
221 sufficient evidence in this study to suggest a greater benefit for the 40 mg/day dose compared to
222 the 20 mg/day dose.

223 Study 2 was a flexible-dose study comparing paroxetine (20 mg to 50 mg daily) and placebo.
224 PAXIL demonstrated statistically significant superiority over placebo on the Hamilton Rating

225 Scale for Anxiety (HAM-A) total score. A third study, also flexible-dose comparing paroxetine
226 (20 mg to 50 mg daily), did not demonstrate statistically significant superiority of PAXIL over
227 placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score, the primary outcome.

228 Subgroup analyses did not indicate differences in treatment outcomes as a function of race or
229 gender. There were insufficient elderly patients to conduct subgroup analyses on the basis of age.

230 In a longer-term trial, 566 patients meeting DSM-IV criteria for Generalized Anxiety
231 Disorder, who had responded during a single-blind, 8-week acute treatment phase with 20 to
232 50 mg/day of PAXIL, were randomized to continuation of PAXIL at their same dose, or to
233 placebo, for up to 24 weeks of observation for relapse. Response during the single-blind phase
234 was defined by having a decrease of ≥ 2 points compared to baseline on the CGI-Severity of
235 Illness scale, to a score of ≤ 3 . Relapse during the double-blind phase was defined as an increase
236 of ≥ 2 points compared to baseline on the CGI-Severity of Illness scale to a score of ≥ 4 , or
237 withdrawal due to lack of efficacy. Patients receiving continued PAXIL experienced a
238 significantly lower relapse rate over the subsequent 24 weeks compared to those receiving
239 placebo.

240 **Posttraumatic Stress Disorder:** The effectiveness of PAXIL in the treatment of
241 Posttraumatic Stress Disorder (PTSD) was demonstrated in two 12-week, multicenter, placebo-
242 controlled studies (Studies 1 and 2) of adult outpatients who met DSM-IV criteria for PTSD. The
243 mean duration of PTSD symptoms for the 2 studies combined was 13 years (ranging from .1 year
244 to 57 years). The percentage of patients with secondary major depressive disorder or non-PTSD
245 anxiety disorders in the combined 2 studies was 41% (356 out of 858 patients) and 40% (345 out
246 of 858 patients), respectively. Study outcome was assessed by (i) the Clinician-Administered
247 PTSD Scale Part 2 (CAPS-2) score and (ii) the Clinical Global Impression-Global Improvement
248 Scale (CGI-I). The CAPS-2 is a multi-item instrument that measures 3 aspects of PTSD with the
249 following symptom clusters: Reexperiencing/intrusion, avoidance/numbing and hyperarousal.
250 The 2 primary outcomes for each trial were (i) change from baseline to endpoint on the CAPS-2
251 total score (17 items), and (ii) proportion of responders on the CGI-I, where responders were
252 defined as patients having a score of 1 (very much improved) or 2 (much improved).

253 Study 1 was a 12-week study comparing fixed paroxetine doses of 20 mg or 40 mg/day to
254 placebo. Doses of 20 mg and 40 mg of PAXIL were demonstrated to be significantly superior to
255 placebo on change from baseline for the CAPS-2 total score and on proportion of responders on
256 the CGI-I. There was not sufficient evidence in this study to suggest a greater benefit for the
257 40 mg/day dose compared to the 20 mg/day dose.

258 Study 2 was a 12-week flexible-dose study comparing paroxetine (20 to 50 mg daily) to
259 placebo. PAXIL was demonstrated to be significantly superior to placebo on change from
260 baseline for the CAPS-2 total score and on proportion of responders on the CGI-I.

261 A third study, also a flexible-dose study comparing paroxetine (20 to 50 mg daily) to placebo,
262 demonstrated PAXIL to be significantly superior to placebo on change from baseline for CAPS-
263 2 total score, but not on proportion of responders on the CGI-I.

264 The majority of patients in these trials were women (68% women: 377 out of 551 subjects in

265 Study 1 and 66% women: 202 out of 303 subjects in Study 2). Subgroup analyses did not
266 indicate differences in treatment outcomes as a function of gender. There were an insufficient
267 number of patients who were 65 years and older or were non-Caucasian to conduct subgroup
268 analyses on the basis of age or race, respectively.

269 **INDICATIONS AND USAGE**

270 **Major Depressive Disorder:** PAXIL is indicated for the treatment of major depressive
271 disorder.

272 The efficacy of PAXIL in the treatment of a major depressive episode was established in
273 6-week controlled trials of outpatients whose diagnoses corresponded most closely to the
274 DSM-III category of major depressive disorder (see CLINICAL PHARMACOLOGY: Clinical
275 Trials). A major depressive episode implies a prominent and relatively persistent depressed or
276 dysphoric mood that usually interferes with daily functioning (nearly every day for at least
277 2 weeks); it should include at least 4 of the following 8 symptoms: Change in appetite, change in
278 sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in
279 sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired
280 concentration, and a suicide attempt or suicidal ideation.

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

282 The efficacy of PAXIL in maintaining a response in major depressive disorder for up to 1 year
283 was demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY: Clinical
284 Trials). Nevertheless, the physician who elects to use PAXIL for extended periods should
285 periodically re-evaluate the long-term usefulness of the drug for the individual patient.

286 **Obsessive Compulsive Disorder:** PAXIL is indicated for the treatment of obsessions and
287 compulsions in patients with obsessive compulsive disorder (OCD) as defined in the DSM-IV.
288 The obsessions or compulsions cause marked distress, are time-consuming, or significantly
289 interfere with social or occupational functioning.

290 The efficacy of PAXIL was established in two 12-week trials with obsessive compulsive
291 outpatients whose diagnoses corresponded most closely to the DSM-III-R category of obsessive
292 compulsive disorder (see CLINICAL PHARMACOLOGY: Clinical Trials).

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

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

302 **Panic Disorder:** PAXIL is indicated for the treatment of panic disorder, with or without
303 agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of

304 unexpected panic attacks and associated concern about having additional attacks, worry about
305 the implications or consequences of the attacks, and/or a significant change in behavior related to
306 the attacks.

307 The efficacy of PAXIL was established in three 10- to 12-week trials in panic disorder
308 patients whose diagnoses corresponded to the DSM-III-R category of panic disorder (see
309 CLINICAL PHARMACOLOGY: Clinical Trials).

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

318 Long-term maintenance of efficacy was demonstrated in a 3-month relapse prevention trial. In
319 this trial, patients with panic disorder assigned to paroxetine demonstrated a lower relapse rate
320 compared to patients on placebo (see CLINICAL PHARMACOLOGY: Clinical Trials).
321 Nevertheless, the physician who prescribes PAXIL for extended periods should periodically
322 re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND
323 ADMINISTRATION).

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

334 The efficacy of PAXIL was established in three 12-week trials in adult patients with social
335 anxiety disorder (DSM-IV). PAXIL has not been studied in children or adolescents with social
336 phobia (see CLINICAL PHARMACOLOGY: Clinical Trials).

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

342 **Generalized Anxiety Disorder:** PAXIL is indicated for the treatment of Generalized Anxiety
343 Disorder (GAD), as defined in DSM-IV. Anxiety or tension associated with the stress of

344 everyday life usually does not require treatment with an anxiolytic.

345 The efficacy of PAXIL in the treatment of GAD was established in two 8-week
346 placebo-controlled trials in adults with GAD. PAXIL has not been studied in children or
347 adolescents with Generalized Anxiety Disorder (see CLINICAL PHARMACOLOGY: Clinical
348 Trials).

349 Generalized Anxiety Disorder (DSM-IV) is characterized by excessive anxiety and worry
350 (apprehensive expectation) that is persistent for at least 6 months and which the person finds
351 difficult to control. It must be associated with at least 3 of the following 6 symptoms:
352 Restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or
353 mind going blank, irritability, muscle tension, sleep disturbance.

354 The efficacy of PAXIL in maintaining a response in patients with Generalized Anxiety
355 Disorder, who responded during an 8-week acute treatment phase while taking PAXIL and were
356 then observed for relapse during a period of up to 24 weeks, was demonstrated in a placebo-
357 controlled trial (see CLINICAL PHARMACOLOGY: Clinical Trials). Nevertheless, the
358 physician who elects to use PAXIL for extended periods should periodically re-evaluate the
359 long-term usefulness of the drug for the individual patient (see DOSAGE AND
360 ADMINISTRATION).

361 **Posttraumatic Stress Disorder:** PAXIL is indicated for the treatment of Posttraumatic
362 Stress Disorder (PTSD).

363 The efficacy of PAXIL in the treatment of PTSD was established in two 12-week placebo-
364 controlled trials in adults with PTSD (DSM-IV) (see CLINICAL PHARMACOLOGY: Clinical
365 Trials).

366 PTSD, as defined by DSM-IV, requires exposure to a traumatic event that involved actual or
367 threatened death or serious injury, or threat to the physical integrity of self or others, and a
368 response that involves intense fear, helplessness, or horror. Symptoms that occur as a result of
369 exposure to the traumatic event include reexperiencing of the event in the form of intrusive
370 thoughts, flashbacks, or dreams, and intense psychological distress and physiological reactivity
371 on exposure to cues to the event; avoidance of situations reminiscent of the traumatic event,
372 inability to recall details of the event, and/or numbing of general responsiveness manifested as
373 diminished interest in significant activities, estrangement from others, restricted range of affect,
374 or sense of foreshortened future; and symptoms of autonomic arousal including hypervigilance,
375 exaggerated startle response, sleep disturbance, impaired concentration, and irritability or
376 outbursts of anger. A PTSD diagnosis requires that the symptoms are present for at least a month
377 and that they cause clinically significant distress or impairment in social, occupational, or other
378 important areas of functioning.

379 The efficacy of PAXIL in longer-term treatment of PTSD, i.e., for more than 12 weeks, has
380 not been systematically evaluated in placebo-controlled trials. Therefore, the physician who
381 elects to prescribe PAXIL for extended periods should periodically re-evaluate the long-term
382 usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

383 **CONTRAINDICATIONS**

384 PAXIL should not be used in patients taking monoamine oxidase inhibitors (MAOIs),
385 including linezolid (an antibiotic which is a reversible non-selective MAOI) and
386 methylthioninium chloride (methylene blue), or within 2 weeks of stopping treatment with
387 MAOIs (see WARNINGS).

388 Concomitant use with thioridazine is contraindicated (see WARNINGS and
389 PRECAUTIONS).

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

391 PAXIL is contraindicated in patients with a hypersensitivity to paroxetine or any of the
392 inactive ingredients in PAXIL.

393 **WARNINGS**

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

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

419

420 **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

421
 422 No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but
 423 the number was not sufficient to reach any conclusion about drug effect on suicide.

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

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

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

438 Consideration should be given to changing the therapeutic regimen, including possibly
 439 discontinuing the medication, in patients whose depression is persistently worse, or who are
 440 experiencing emergent suicidality or symptoms that might be precursors to worsening depression
 441 or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the
 442 patient’s presenting symptoms.

443 If the decision has been made to discontinue treatment, medication should be tapered, as
 444 rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with
 445 certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION:
 446 Discontinuation of Treatment With PAXIL, for a description of the risks of discontinuation of
 447 PAXIL).

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

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

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

465 **Potential for Interaction With Monoamine Oxidase Inhibitors:** In patients receiving
466 another serotonin reuptake inhibitor drug in combination with a monoamine oxidase
467 inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including
468 hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of
469 vital signs, and mental status changes that include extreme agitation progressing to
470 delirium and coma. These reactions have also been reported in patients who have recently
471 discontinued that drug and have been started on an MAOI. Some cases presented with
472 features resembling neuroleptic malignant syndrome. While there are no human data
473 showing such an interaction with PAXIL, limited animal data on the effects of combined
474 use of paroxetine and MAOIs suggest that these drugs may act synergistically to elevate
475 blood pressure and evoke behavioral excitation. Therefore, it is recommended that PAXIL
476 not be used in combination with an MAOI (including linezolid, an antibiotic which is a
477 reversible non-selective MAOI), and methylthioninium chloride [methylene blue]), or
478 within 14 days of discontinuing treatment with an MAOI (see CONTRAINDICATIONS).

479 **At least 2 weeks should be allowed after stopping PAXIL before starting an MAOI.**
480 **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions:**
481 **The development of a potentially life-threatening serotonin syndrome or Neuroleptic**
482 **Malignant Syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs**
483 **alone, including treatment with PAXIL, but particularly with concomitant use of**
484 **serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin**
485 **(including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin**
486 **syndrome symptoms may include mental status changes (e.g., agitation, hallucinations,**
487 **coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia),**
488 **neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal**
489 **symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form**
490 **can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle**
491 **rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental**

492 status changes. Patients should be monitored for the emergence of serotonin syndrome or
493 NMS-like signs and symptoms.

494 The concomitant use of PAXIL with MAOIs intended to treat depression is
495 contraindicated.

496 If concomitant treatment of PAXIL with a 5-hydroxytryptamine receptor agonist
497 (triptan) is clinically warranted, careful observation of the patient is advised, particularly
498 during treatment initiation and dose increases.

499 The concomitant use of PAXIL with serotonin precursors (such as tryptophan) is not
500 recommended.

501 Treatment with PAXIL and any concomitant serotonergic or antidopaminergic agents,
502 including antipsychotics, should be discontinued immediately if the above events occur and
503 supportive symptomatic treatment should be initiated.

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

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

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

- 516 • A study based on Swedish national registry data demonstrated that infants exposed to
517 paroxetine during pregnancy (n = 815) had an increased risk of cardiovascular
518 malformations (2% risk in paroxetine-exposed infants) compared to the entire registry
519 population (1% risk), for an odds ratio (OR) of 1.8 (95% confidence interval 1.1 to 2.8). No
520 increase in the risk of overall congenital malformations was seen in the paroxetine-exposed
521 infants. The cardiac malformations in the paroxetine-exposed infants were primarily
522 ventricular septal defects (VSDs) and atrial septal defects (ASDs). Septal defects range in
523 severity from those that resolve spontaneously to those which require surgery.
- 524 • A separate retrospective cohort study from the United States (United Healthcare data)
525 evaluated 5,956 infants of mothers dispensed antidepressants during the first trimester
526 (n = 815 for paroxetine). This study showed a trend towards an increased risk for
527 cardiovascular malformations for paroxetine (risk of 1.5%) compared to other
528 antidepressants (risk of 1%), for an OR of 1.5 (95% confidence interval 0.8 to 2.9). Of the
529 12 paroxetine-exposed infants with cardiovascular malformations, 9 had VSDs. This study
530 also suggested an increased risk of overall major congenital malformations including
531 cardiovascular defects for paroxetine (4% risk) compared to other (2% risk) antidepressants

532 (OR 1.8; 95% confidence interval 1.2 to 2.8).

- 533 • Two large case-control studies using separate databases, each with >9,000 birth defect
534 cases and >4,000 controls, found that maternal use of paroxetine during the first trimester
535 of pregnancy was associated with a 2- to 3-fold increased risk of right ventricular outflow
536 tract obstructions. In one study the odds ratio was 2.5 (95% confidence interval, 1.0 to 6.0,
537 7 exposed infants) and in the other study the odds ratio was 3.3 (95% confidence interval,
538 1.3 to 8.8, 6 exposed infants).

539 Other studies have found varying results as to whether there was an increased risk of overall,
540 cardiovascular, or specific congenital malformations. A meta-analysis of epidemiological data
541 over a 16-year period (1992 to 2008) on first trimester paroxetine use in pregnancy and
542 congenital malformations included the above-noted studies in addition to others (n = 17 studies
543 that included overall malformations and n = 14 studies that included cardiovascular
544 malformations; n = 20 distinct studies). While subject to limitations, this meta-analysis suggested
545 an increased occurrence of cardiovascular malformations (prevalence odds ratio [POR] 1.5; 95%
546 confidence interval 1.2 to 1.9) and overall malformations (POR 1.2; 95% confidence interval 1.1
547 to 1.4) with paroxetine use during the first trimester. It was not possible in this meta-analysis to
548 determine the extent to which the observed prevalence of cardiovascular malformations might
549 have contributed to that of overall malformations, nor was it possible to determine whether any
550 specific types of cardiovascular malformations might have contributed to the observed
551 prevalence of all cardiovascular malformations.

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

558 **Animal Findings:** Reproduction studies were performed at doses up to 50 mg/kg/day in rats
559 and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately
560 8 (rat) and 2 (rabbit) times the maximum recommended human dose (MRHD) on an mg/m²
561 basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was
562 an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last
563 trimester of gestation and continued throughout lactation. This effect occurred at a dose of
564 1 mg/kg/day or approximately one-sixth of the MRHD on an mg/m² basis. The no-effect dose for
565 rat pup mortality was not determined. The cause of these deaths is not known.

566 **Nonteratogenic Effects:** Neonates exposed to PAXIL and other SSRIs or serotonin and
567 norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed
568 complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such
569 complications can arise immediately upon delivery. Reported clinical findings have included
570 respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty,
571 vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and

572 constant crying. These features are consistent with either a direct toxic effect of SSRIs and
573 SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the
574 clinical picture is consistent with serotonin syndrome (see WARNINGS: Serotonin Syndrome or
575 Neuroleptic Malignant Syndrome (NMS)-like Reactions).

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

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

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

594 PRECAUTIONS

595 **General: Activation of Mania/Hypomania:** During premarketing testing, hypomania or
596 mania occurred in approximately 1.0% of unipolar patients treated with PAXIL compared to
597 1.1% of active-control and 0.3% of placebo-treated unipolar patients. In a subset of patients
598 classified as bipolar, the rate of manic episodes was 2.2% for PAXIL and 11.6% for the
599 combined active-control groups. As with all drugs effective in the treatment of major depressive
600 disorder, PAXIL should be used cautiously in patients with a history of mania.

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

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

611 With this regimen in those studies, the following adverse events were reported at an incidence
612 of 2% or greater for PAXIL and were at least twice that reported for placebo: Abnormal dreams,
613 paresthesia, and dizziness. In the majority of patients, these events were mild to moderate and
614 were self-limiting and did not require medical intervention.

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

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

627 See also PRECAUTIONS: Pediatric Use, for adverse events reported upon discontinuation of
628 treatment with PAXIL in pediatric patients.

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

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

641 **Hyponatremia:** Hyponatremia may occur as a result of treatment with SSRIs and SNRIs,
642 including PAXIL. In many cases, this hyponatremia appears to be the result of the syndrome of
643 inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than
644 110 mmol/L have been reported. Elderly patients may be at greater risk of developing
645 hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise
646 volume depleted may be at greater risk (see PRECAUTIONS: Geriatric Use). Discontinuation of
647 PAXIL should be considered in patients with symptomatic hyponatremia and appropriate
648 medical intervention should be instituted.

649 Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory
650 impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and

651 symptoms associated with more severe and/or acute cases have included hallucination, syncope,
652 seizure, coma, respiratory arrest, and death.

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

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

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

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

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

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

687 **Information for Patients:** PAXIL should not be chewed or crushed, and should be swallowed
688 whole.

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

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

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

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

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

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

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

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

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

730 **Pregnancy:** Patients should be advised to notify their physician if they become pregnant or

731 intend to become pregnant during therapy (see WARNINGS: Usage in Pregnancy: *Teratogenic*
732 and *Nonteratogenic Effects*).

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

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

736 **Drug Interactions: Tryptophan:** As with other serotonin reuptake inhibitors, an interaction
737 between paroxetine and tryptophan may occur when they are coadministered. Adverse
738 experiences, consisting primarily of headache, nausea, sweating, and dizziness, have been
739 reported when tryptophan was administered to patients taking PAXIL. Consequently,
740 concomitant use of PAXIL with tryptophan is not recommended (see WARNINGS: Serotonin
741 Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions).

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

743 **Pimozide:** In a controlled study of healthy volunteers, after PAXIL was titrated to 60 mg
744 daily, co-administration of a single dose of 2 mg pimozide was associated with mean increases in
745 pimozide AUC of 151% and C_{max} of 62%, compared to pimozide administered alone. The
746 increase in pimozide AUC and C_{max} is due to the CYP2D6 inhibitory properties of paroxetine.
747 Due to the narrow therapeutic index of pimozide and its known ability to prolong the QT
748 interval, concomitant use of pimozide and PAXIL is contraindicated (see
749 CONTRAINDICATIONS).

750 **Serotonergic Drugs:** Based on the mechanism of action of SNRIs and SSRIs, including
751 paroxetine hydrochloride, and the potential for serotonin syndrome, caution is advised when
752 PAXIL is coadministered with other drugs that may affect the serotonergic neurotransmitter
753 systems, such as triptans, lithium, fentanyl, tramadol, or St. John's Wort (see WARNINGS:
754 Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions).

755 The concomitant use of PAXIL with MAOIs (including linezolid and methylene blue) is
756 contraindicated (see CONTRAINDICATIONS). The concomitant use of PAXIL with other
757 SSRIs, SNRIs or tryptophan is not recommended (see PRECAUTIONS: Drug Interactions:
758 *Tryptophan*).

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

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

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

770 **Drugs Affecting Hepatic Metabolism:** The metabolism and pharmacokinetics of

771 paroxetine may be affected by the induction or inhibition of drug-metabolizing enzymes.

772 **Cimetidine:** Cimetidine inhibits many cytochrome P₄₅₀ (oxidative) enzymes. In a study
773 where PAXIL (30 mg once daily) was dosed orally for 4 weeks, steady-state plasma
774 concentrations of paroxetine were increased by approximately 50% during coadministration with
775 oral cimetidine (300 mg three times daily) for the final week. Therefore, when these drugs are
776 administered concurrently, dosage adjustment of PAXIL after the 20-mg starting dose should be
777 guided by clinical effect. The effect of paroxetine on cimetidine's pharmacokinetics was not
778 studied.

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

788 **Phenytoin:** When a single oral 30-mg dose of PAXIL was administered at phenytoin steady
789 state (300 mg once daily for 14 days), paroxetine AUC and T_{1/2} were reduced (by an average of
790 50% and 35%, respectively) compared to PAXIL administered alone. In a separate study, when a
791 single oral 300-mg dose of phenytoin was administered at paroxetine steady state (30 mg once
792 daily for 14 days), phenytoin AUC was slightly reduced (12% on average) compared to
793 phenytoin administered alone. Since both drugs exhibit nonlinear pharmacokinetics, the above
794 studies may not address the case where the 2 drugs are both being chronically dosed. No initial
795 dosage adjustments are considered necessary when these drugs are coadministered; any
796 subsequent adjustments should be guided by clinical effect (see ADVERSE REACTIONS:
797 Postmarketing Reports).

798 **Drugs Metabolized by CYP2D6:** Many drugs, including most drugs effective in the
799 treatment of major depressive disorder (paroxetine, other SSRIs and many tricyclics), are
800 metabolized by the cytochrome P₄₅₀ isozyme CYP2D6. Like other agents that are metabolized by
801 CYP2D6, paroxetine may significantly inhibit the activity of this isozyme. In most patients
802 (>90%), this CYP2D6 isozyme is saturated early during dosing with PAXIL. In 1 study, daily
803 dosing of PAXIL (20 mg once daily) under steady-state conditions increased single dose
804 desipramine (100 mg) C_{max}, AUC, and T_{1/2} by an average of approximately 2-, 5-, and 3-fold,
805 respectively. Concomitant use of paroxetine with risperidone, a CYP2D6 substrate has also been
806 evaluated. In 1 study, daily dosing of paroxetine 20 mg in patients stabilized on risperidone (4 to
807 8 mg/day) increased mean plasma concentrations of risperidone approximately 4-fold, decreased
808 9-hydroxyrisperidone concentrations approximately 10%, and increased concentrations of the
809 active moiety (the sum of risperidone plus 9-hydroxyrisperidone) approximately 1.4-fold. The
810 effect of paroxetine on the pharmacokinetics of atomoxetine has been evaluated when both drugs

811 were at steady state. In healthy volunteers who were extensive metabolizers of CYP2D6,
812 paroxetine 20 mg daily was given in combination with 20 mg atomoxetine every 12 hours. This
813 resulted in increases in steady state atomoxetine AUC values that were 6- to 8-fold greater and in
814 atomoxetine C_{max} values that were 3- to 4-fold greater than when atomoxetine was given alone.
815 Dosage adjustment of atomoxetine may be necessary and it is recommended that atomoxetine be
816 initiated at a reduced dose when it is given with paroxetine.

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

820 Therefore, coadministration of PAXIL with other drugs that are metabolized by this isozyme,
821 including certain drugs effective in the treatment of major depressive disorder (e.g., nortriptyline,
822 amitriptyline, imipramine, desipramine, and fluoxetine), phenothiazines, risperidone, and Type
823 1C antiarrhythmics (e.g., propafenone, flecainide, and encainide), or that inhibit this enzyme
824 (e.g., quinidine), should be approached with caution.

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

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

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

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

844 **Tricyclic Antidepressants (TCAs):** Caution is indicated in the coadministration of
845 tricyclic antidepressants (TCAs) with PAXIL, because paroxetine may inhibit TCA metabolism.
846 Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be
847 reduced, if a TCA is coadministered with PAXIL (see PRECAUTIONS: *Drugs Metabolized by*
848 *Cytochrome CYP2D6*).

849 **Drugs Highly Bound to Plasma Protein:** Because paroxetine is highly bound to plasma
850 protein, administration of PAXIL to a patient taking another drug that is highly protein bound

851 may cause increased free concentrations of the other drug, potentially resulting in adverse events.
852 Conversely, adverse effects could result from displacement of paroxetine by other highly bound
853 drugs.

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

855 Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of
856 the case-control and cohort design that have demonstrated an association between use of
857 psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper
858 gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may
859 potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have
860 been reported when SSRIs or SNRIs are coadministered with warfarin. Patients receiving
861 warfarin therapy should be carefully monitored when paroxetine is initiated or discontinued.

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

864 ***Lithium:*** A multiple-dose study has shown that there is no pharmacokinetic interaction
865 between PAXIL and lithium carbonate. However, due to the potential for serotonin syndrome,
866 caution is advised when PAXIL is coadministered with lithium.

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

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

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

877 ***Beta-Blockers:*** In a study where propranolol (80 mg twice daily) was dosed orally for
878 18 days, the established steady-state plasma concentrations of propranolol were unaltered during
879 coadministration with PAXIL (30 mg once daily) for the final 10 days. The effects of
880 propranolol on paroxetine have not been evaluated (see ADVERSE REACTIONS:
881 Postmarketing Reports).

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

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

889 ***Electroconvulsive Therapy (ECT):*** There are no clinical studies of the combined use of
890 ECT and PAXIL.

891 **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** Two-year
892 carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and
893 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to 2.4 (mouse) and
894 3.9 (rat) times the MRHD for major depressive disorder, social anxiety disorder, GAD, and
895 PTSD on a mg/m² basis. Because the MRHD for major depressive disorder is slightly less than
896 that for OCD (50 mg versus 60 mg), the doses used in these carcinogenicity studies were only
897 2.0 (mouse) and 3.2 (rat) times the MRHD for OCD. There was a significantly greater number of
898 male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50, and 4/50 for
899 control, low-, middle-, and high-dose groups, respectively) and a significantly increased linear
900 trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats
901 were not affected. Although there was a dose-related increase in the number of tumors in mice,
902 there was no drug-related increase in the number of mice with tumors. The relevance of these
903 findings to humans is unknown.

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

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

911 A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of
912 15 mg/kg/day, which is 2.9 times the MRHD for major depressive disorder, social anxiety
913 disorder, GAD, and PTSD or 2.4 times the MRHD for OCD on a mg/m² basis. Irreversible
914 lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to
915 52 weeks. These lesions consisted of vacuolation of epididymal tubular epithelium at
916 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with arrested
917 spermatogenesis at 25 mg/kg/day (9.8 and 4.9 times the MRHD for major depressive disorder,
918 social anxiety disorder, and GAD; 8.2 and 4.1 times the MRHD for OCD and PD on a mg/m²
919 basis).

920 **Pregnancy:** Pregnancy Category D. See WARNINGS: Usage in Pregnancy: *Teratogenic* and
921 *Nonteratogenic Effects*.

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

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

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

930 Decreased appetite and weight loss have been observed in association with the use of SSRIs.

931 Consequently, regular monitoring of weight and growth should be performed in children and
932 adolescents treated with an SSRI such as Paxil.

933 In placebo-controlled clinical trials conducted with pediatric patients, the following adverse
934 events were reported in at least 2% of pediatric patients treated with PAXIL and occurred at a
935 rate at least twice that for pediatric patients receiving placebo: emotional lability (including self-
936 harm, suicidal thoughts, attempted suicide, crying, and mood fluctuations), hostility, decreased
937 appetite, tremor, sweating, hyperkinesia, and agitation.

938 Events reported upon discontinuation of treatment with PAXIL in the pediatric clinical trials
939 that included a taper phase regimen, which occurred in at least 2% of patients who received
940 PAXIL and which occurred at a rate at least twice that of placebo, were: emotional lability
941 (including suicidal ideation, suicide attempt, mood changes, and tearfulness), nervousness,
942 dizziness, nausea, and abdominal pain (see DOSAGE AND ADMINISTRATION:
943 Discontinuation of Treatment With PAXIL).

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

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

953 **ADVERSE REACTIONS**

954 **Associated With Discontinuation of Treatment:** Twenty percent (1,199/6,145) of patients
955 treated with PAXIL in worldwide clinical trials in major depressive disorder and 16.1%
956 (84/522), 11.8% (64/542), 9.4% (44/469), 10.7% (79/735), and 11.7% (79/676) of patients
957 treated with PAXIL in worldwide trials in social anxiety disorder, OCD, panic disorder, GAD,
958 and PTSD, respectively, discontinued treatment due to an adverse event. The most common
959 events ($\geq 1\%$) associated with discontinuation and considered to be drug related (i.e., those events
960 associated with dropout at a rate approximately twice or greater for PAXIL compared to placebo)
961 included the following:
962

	Major Depressive Disorder		OCD		Panic Disorder		Social Anxiety Disorder		Generalized Anxiety Disorder		PTSD	
	PAXIL	Placebo	PAXIL	Placebo	PAXIL	Placebo	PAXIL	Placebo	PAXIL	Placebo	PAXIL	Placebo
CNS												
Somnolence	2.3%	0.7%	—		1.9%	0.3%	3.4%	0.3%	2.0%	0.2%	2.8%	0.6%
Insomnia	—	—	1.7%	0%	1.3%	0.3%	3.1%	0%			—	—
Agitation	1.1%	0.5%	—								—	—
Tremor	1.1%	0.3%	—				1.7%	0%			1.0%	0.2%
Anxiety	—	—	—				1.1%	0%			—	—
Dizziness	—	—	1.5%	0%			1.9%	0%	1.0%	0.2%	—	—
Gastrointestinal												
Constipation	—		1.1%	0%							—	—
Nausea	3.2%	1.1%	1.9%	0%	3.2%	1.2%	4.0%	0.3%	2.0%	0.2%	2.2%	0.6%
Diarrhea	1.0%	0.3%	—								—	—
Dry mouth	1.0%	0.3%	—								—	—
Vomiting	1.0%	0.3%	—				1.0%	0%			—	—
Flatulence							1.0%	0.3%			—	—
Other												
Asthenia	1.6%	0.4%	1.9%	0.4%			2.5%	0.6%	1.8%	0.2%	1.6%	0.2%
Abnormal Ejaculation ^a	1.6%	0%	2.1%	0%			4.9%	0.6%	2.5%	0.5%	—	—
Sweating	1.0%	0.3%	—				1.1%	0%	1.1%	0.2%	—	—
Impotence ^a	—		1.5%	0%							—	—
Libido Decreased							1.0%	0%			—	—

963 Where numbers are not provided the incidence of the adverse events in patients treated with
964 PAXIL was not >1% or was not greater than or equal to 2 times the incidence of placebo.

965 a. Incidence corrected for gender.

966

967 **Commonly Observed Adverse Events: Major Depressive Disorder:** The most
968 commonly observed adverse events associated with the use of paroxetine (incidence of 5% or
969 greater and incidence for PAXIL at least twice that for placebo, derived from Table 2) were:
970 Asthenia, sweating, nausea, decreased appetite, somnolence, dizziness, insomnia, tremor,
971 nervousness, ejaculatory disturbance, and other male genital disorders.

972 **Obsessive Compulsive Disorder:** The most commonly observed adverse events
973 associated with the use of paroxetine (incidence of 5% or greater and incidence for PAXIL at
974 least twice that of placebo, derived from Table 3) were: Nausea, dry mouth, decreased appetite,
975 constipation, dizziness, somnolence, tremor, sweating, impotence, and abnormal ejaculation.

976 **Panic Disorder:** The most commonly observed adverse events associated with the use of
977 paroxetine (incidence of 5% or greater and incidence for PAXIL at least twice that for placebo,
978 derived from Table 3) were: Asthenia, sweating, decreased appetite, libido decreased, tremor,

979 abnormal ejaculation, female genital disorders, and impotence.

980 **Social Anxiety Disorder:** The most commonly observed adverse events associated with
981 the use of paroxetine (incidence of 5% or greater and incidence for PAXIL at least twice that for
982 placebo, derived from Table 3) were: Sweating, nausea, dry mouth, constipation, decreased
983 appetite, somnolence, tremor, libido decreased, yawn, abnormal ejaculation, female genital
984 disorders, and impotence.

985 **Generalized Anxiety Disorder:** The most commonly observed adverse events associated
986 with the use of paroxetine (incidence of 5% or greater and incidence for PAXIL at least twice
987 that for placebo, derived from Table 4) were: Asthenia, infection, constipation, decreased
988 appetite, dry mouth, nausea, libido decreased, somnolence, tremor, sweating, and abnormal
989 ejaculation.

990 **Posttraumatic Stress Disorder:** The most commonly observed adverse events associated
991 with the use of paroxetine (incidence of 5% or greater and incidence for PAXIL at least twice
992 that for placebo, derived from Table 4) were: Asthenia, sweating, nausea, dry mouth, diarrhea,
993 decreased appetite, somnolence, libido decreased, abnormal ejaculation, female genital disorders,
994 and impotence.

995 **Incidence in Controlled Clinical Trials:** The prescriber should be aware that the figures in
996 the tables following cannot be used to predict the incidence of side effects in the course of usual
997 medical practice where patient characteristics and other factors differ from those that prevailed in
998 the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from
999 other clinical investigations involving different treatments, uses, and investigators. The cited
1000 figures, however, do provide the prescribing physician with some basis for estimating the
1001 relative contribution of drug and nondrug factors to the side effect incidence rate in the
1002 populations studied.

1003 **Major Depressive Disorder:** Table 2 enumerates adverse events that occurred at an
1004 incidence of 1% or more among paroxetine-treated patients who participated in short-term
1005 (6-week) placebo-controlled trials in which patients were dosed in a range of 20 mg to
1006 50 mg/day. Reported adverse events were classified using a standard COSTART-based
1007 Dictionary terminology.

1008

1009 **Table 2. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled**
 1010 **Clinical Trials for Major Depressive Disorder^a**

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

1011 a. Events reported by at least 1% of patients treated with PAXIL are included, except the
 1012 following events which had an incidence on placebo \geq PAXIL: Abdominal pain, agitation,
 1013 back pain, chest pain, CNS stimulation, fever, increased appetite, myoclonus, pharyngitis,
 1014 postural hypotension, respiratory disorder (includes mostly “cold symptoms” or “URI”),
 1015 trauma, and vomiting.

1016 b. Includes mostly “lump in throat” and “tightness in throat.”

- 1017 c. Percentage corrected for gender.
 1018 d. Mostly “ejaculatory delay.”
 1019 e. Includes “anorgasmia,” “erectile difficulties,” “delayed ejaculation/orgasm,” and “sexual
 1020 dysfunction,” and “impotence.”
 1021 f. Includes mostly “difficulty with micturition” and “urinary hesitancy.”
 1022 g. Includes mostly “anorgasmia” and “difficulty reaching climax/orgasm.”
 1023

Obsessive Compulsive Disorder, Panic Disorder, and Social Anxiety Disorder:

1025 Table 3 enumerates adverse events that occurred at a frequency of 2% or more among OCD
 1026 patients on PAXIL who participated in placebo-controlled trials of 12-weeks duration in which
 1027 patients were dosed in a range of 20 mg to 60 mg/day or among patients with panic disorder on
 1028 PAXIL who participated in placebo-controlled trials of 10- to 12-weeks duration in which
 1029 patients were dosed in a range of 10 mg to 60 mg/day or among patients with social anxiety
 1030 disorder on PAXIL who participated in placebo-controlled trials of 12-weeks duration in which
 1031 patients were dosed in a range of 20 mg to 50 mg/day.
 1032

**Table 3. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled
 Clinical Trials for Obsessive Compulsive Disorder, Panic Disorder, and Social Anxiety
 Disorder^a**

Body System	Preferred Term	Obsessive Compulsive Disorder		Panic Disorder		Social Anxiety Disorder	
		PAXIL (n = 542)	Placebo (n = 265)	PAXIL (n = 469)	Placebo (n = 324)	PAXIL (n = 425)	Placebo (n = 339)
Body as a Whole	Asthenia	22%	14%	14%	5%	22%	14%
	Abdominal Pain	—	—	4%	3%	—	—
	Chest Pain	3%	2%	—	—	—	—
	Back Pain	—	—	3%	2%	—	—
	Chills	2%	1%	2%	1%	—	—
	Trauma	—	—	—	—	3%	1%
Cardiovascular	Vasodilation	4%	1%	—	—	—	—
	Palpitation	2%	0%	—	—	—	—
Dermatologic	Sweating	9%	3%	14%	6%	9%	2%
	Rash	3%	2%	—	—	—	—
Gastrointestinal	Nausea	23%	10%	23%	17%	25%	7%
	Dry Mouth	18%	9%	18%	11%	9%	3%
	Constipation	16%	6%	8%	5%	5%	2%
	Diarrhea	10%	10%	12%	7%	9%	6%
	Decreased Appetite	9%	3%	7%	3%	8%	2%
	Dyspepsia	—	—	—	—	4%	2%
	Flatulence	—	—	—	—	4%	2%
	Increased	—	—	—	—	—	—

		Obsessive Compulsive Disorder		Panic Disorder		Social Anxiety Disorder	
		4%	3%	2%	1%	—	—
	Appetite	4%	3%	2%	1%	—	—
	Vomiting	—	—	—	—	2%	1%
Musculoskeletal	Myalgia	—	—	—	—	4%	3%
Nervous System	Insomnia	24%	13%	18%	10%	21%	16%
	Somnolence	24%	7%	19%	11%	22%	5%
	Dizziness	12%	6%	14%	10%	11%	7%
	Tremor	11%	1%	9%	1%	9%	1%
	Nervousness	9%	8%	—	—	8%	7%
	Libido Decreased	7%	4%	9%	1%	12%	1%
	Agitation	—	—	5%	4%	3%	1%
	Anxiety	—	—	5%	4%	5%	4%
	Abnormal Dreams	4%	1%	—	—	—	—
	Concentration Impaired	3%	2%	—	—	4%	1%
	Depersonalization	3%	0%	—	—	—	—
	Myoclonus	3%	0%	3%	2%	2%	1%
	Amnesia	2%	1%	—	—	—	—
	Respiratory System	Rhinitis	—	—	3%	0%	—
Pharyngitis		—	—	—	—	4%	2%
Yawn		—	—	—	—	5%	1%
Special Senses	Abnormal Vision	4%	2%	—	—	4%	1%
	Taste Perversion	2%	0%	—	—	—	—
Urogenital System	Abnormal Ejaculation ^b	23%	1%	21%	1%	28%	1%
	Dysmenorrhea	—	—	—	—	5%	4%
	Female Genital Disorder ^b	3%	0%	9%	1%	9%	1%
	Impotence ^b	8%	1%	5%	0%	5%	1%
	Urinary Frequency	3%	1%	2%	0%	—	—
	Urination Impaired	3%	0%	—	—	—	—
	Urinary Tract Infection	2%	1%	2%	1%	—	—

1036 a. Events reported by at least 2% of OCD, panic disorder, and social anxiety disorder in patients
1037 treated with PAXIL are included, except the following events which had an incidence on
1038 placebo \geq PAXIL: [OCD]: Abdominal pain, agitation, anxiety, back pain, cough increased,
1039 depression, headache, hyperkinesia, infection, paresthesia, pharyngitis, respiratory disorder,
1040 rhinitis, and sinusitis. [panic disorder]: Abnormal dreams, abnormal vision, chest pain, cough
1041 increased, depersonalization, depression, dysmenorrhea, dyspepsia, flu syndrome, headache,

1042 infection, myalgia, nervousness, palpitation, paresthesia, pharyngitis, rash, respiratory
1043 disorder, sinusitis, taste perversion, trauma, urination impaired, and vasodilation. [social
1044 anxiety disorder]: Abdominal pain, depression, headache, infection, respiratory disorder, and
1045 sinusitis.

1046 b. Percentage corrected for gender.

1047

1048 **Generalized Anxiety Disorder and Posttraumatic Stress Disorder:** Table 4
1049 enumerates adverse events that occurred at a frequency of 2% or more among GAD patients on
1050 PAXIL who participated in placebo-controlled trials of 8-weeks duration in which patients were
1051 dosed in a range of 10 mg/day to 50 mg/day or among PTSD patients on PAXIL who
1052 participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a
1053 range of 20 mg/day to 50 mg/day.

1054

1055 **Table 4. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled**
 1056 **Clinical Trials for Generalized Anxiety Disorder and Posttraumatic Stress Disorder^a**

Body System	Preferred Term	Generalized Anxiety Disorder		Posttraumatic Stress Disorder	
		PAXIL (n = 735)	Placebo (n = 529)	PAXIL (n = 676)	Placebo (n = 504)
Body as a Whole	Asthenia	14%	6%	12%	4%
	Headache	17%	14%	—	—
	Infection	6%	3%	5%	4%
	Abdominal Pain			4%	3%
	Trauma			6%	5%
Cardiovascular	Vasodilation	3%	1%	2%	1%
Dermatologic	Sweating	6%	2%	5%	1%
Gastrointestinal	Nausea	20%	5%	19%	8%
	Dry Mouth	11%	5%	10%	5%
	Constipation	10%	2%	5%	3%
	Diarrhea	9%	7%	11%	5%
	Decreased Appetite	5%	1%	6%	3%
	Vomiting	3%	2%	3%	2%
	Dyspepsia	—	—	5%	3%
Nervous System	Insomnia	11%	8%	12%	11%
	Somnolence	15%	5%	16%	5%
	Dizziness	6%	5%	6%	5%
	Tremor	5%	1%	4%	1%
	Nervousness	4%	3%	—	—
	Libido Decreased	9%	2%	5%	2%
	Abnormal Dreams			3%	2%
Respiratory System	Respiratory Disorder	7%	5%	—	—
	Sinusitis	4%	3%	—	—
	Yawn	4%	—	2%	<1%
Special Senses	Abnormal Vision	2%	1%	3%	1%
Urogenital System	Abnormal Ejaculation ^b	25%	2%	13%	2%
	Female Genital Disorder ^b	4%	1%	5%	1%
	Impotence ^b	4%	3%	9%	1%

- 1057 a. Events reported by at least 2% of GAD and PTSD in patients treated with PAXIL are
 1058 included, except the following events which had an incidence on placebo \geq PAXIL [GAD]:
 1059 Abdominal pain, back pain, trauma, dyspepsia, myalgia, and pharyngitis. [PTSD]: Back pain,
 1060 headache, anxiety, depression, nervousness, respiratory disorder, pharyngitis, and sinusitis.
 1061 b. Percentage corrected for gender.

1062
 1063 **Dose Dependency of Adverse Events:** A comparison of adverse event rates in a
 1064 fixed-dose study comparing 10, 20, 30, and 40 mg/day of PAXIL with placebo in the treatment
 1065 of major depressive disorder revealed a clear dose dependency for some of the more common
 1066 adverse events associated with use of PAXIL, as shown in Table 5:

1067
1068
1069

Table 5 . Treatment-Emergent Adverse Experience Incidence in a Dose-Comparison Trial in the Treatment of Major Depressive Disorder^a

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

1070 a. Rule for including adverse events in table: Incidence at least 5% for 1 of paroxetine groups
1071 and \geq twice the placebo incidence for at least 1 paroxetine group.

1072
1073 In a fixed-dose study comparing placebo and 20, 40, and 60 mg of PAXIL in the treatment of
1074 OCD, there was no clear relationship between adverse events and the dose of PAXIL to which
1075 patients were assigned. No new adverse events were observed in the group treated with 60 mg of
1076 PAXIL compared to any of the other treatment groups.

1077 In a fixed-dose study comparing placebo and 10, 20, and 40 mg of PAXIL in the treatment of
1078 panic disorder, there was no clear relationship between adverse events and the dose of PAXIL to
1079 which patients were assigned, except for asthenia, dry mouth, anxiety, libido decreased, tremor,
1080 and abnormal ejaculation. In flexible-dose studies, no new adverse events were observed in
1081 patients receiving 60 mg of PAXIL compared to any of the other treatment groups.

1082 In a fixed-dose study comparing placebo and 20, 40, and 60 mg of PAXIL in the treatment of
1083 social anxiety disorder, for most of the adverse events, there was no clear relationship between

1084 adverse events and the dose of PAXIL to which patients were assigned.

1085 In a fixed-dose study comparing placebo and 20 and 40 mg of PAXIL in the treatment of
1086 generalized anxiety disorder, for most of the adverse events, there was no clear relationship
1087 between adverse events and the dose of PAXIL to which patients were assigned, except for the
1088 following adverse events: Asthenia, constipation, and abnormal ejaculation.

1089 In a fixed-dose study comparing placebo and 20 and 40 mg of PAXIL in the treatment of
1090 posttraumatic stress disorder, for most of the adverse events, there was no clear relationship
1091 between adverse events and the dose of PAXIL to which patients were assigned, except for
1092 impotence and abnormal ejaculation.

1093 **Adaptation to Certain Adverse Events:** Over a 4- to 6-week period, there was evidence
1094 of adaptation to some adverse events with continued therapy (e.g., nausea and dizziness), but less
1095 to other effects (e.g., dry mouth, somnolence, and asthenia).

1096 **Male and Female Sexual Dysfunction With SSRIs:** Although changes in sexual desire,
1097 sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric
1098 disorder, they may also be a consequence of pharmacologic treatment. In particular, some
1099 evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward
1100 sexual experiences.

1101 Reliable estimates of the incidence and severity of untoward experiences involving sexual
1102 desire, performance, and satisfaction are difficult to obtain, however, in part because patients and
1103 physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of
1104 untoward sexual experience and performance cited in product labeling, are likely to
1105 underestimate their actual incidence.

1106 In placebo-controlled clinical trials involving more than 3,200 patients, the ranges for the
1107 reported incidence of sexual side effects in males and females with major depressive disorder,
1108 OCD, panic disorder, social anxiety disorder, GAD, and PTSD are displayed in Table 6.

1109

1110

Table 6. Incidence of Sexual Adverse Events in Controlled Clinical Trials

	PAXIL	Placebo
n (males)	1446	1042
Decreased Libido	6-15%	0-5%
Ejaculatory Disturbance	13-28%	0-2%
Impotence	2-9%	0-3%
n (females)	1822	1340
Decreased Libido	0-9%	0-2%
Orgasmic Disturbance	2-9%	0-1%

1111

1112 There are no adequate and well-controlled studies examining sexual dysfunction with
1113 paroxetine treatment.

1114 Paroxetine treatment has been associated with several cases of priapism. In those cases with a
1115 known outcome, patients recovered without sequelae.

1116 While it is difficult to know the precise risk of sexual dysfunction associated with the use of

1117 SSRIs, physicians should routinely inquire about such possible side effects.

1118 **Weight and Vital Sign Changes:** Significant weight loss may be an undesirable result of
1119 treatment with PAXIL for some patients but, on average, patients in controlled trials had minimal
1120 (about 1 pound) weight loss versus smaller changes on placebo and active control. No significant
1121 changes in vital signs (systolic and diastolic blood pressure, pulse and temperature) were
1122 observed in patients treated with PAXIL in controlled clinical trials.

1123 **ECG Changes:** In an analysis of ECGs obtained in 682 patients treated with PAXIL and
1124 415 patients treated with placebo in controlled clinical trials, no clinically significant changes
1125 were seen in the ECGs of either group.

1126 **Liver Function Tests:** In placebo-controlled clinical trials, patients treated with PAXIL
1127 exhibited abnormal values on liver function tests at no greater rate than that seen in
1128 placebo-treated patients. In particular, the PAXIL-versus-placebo comparisons for alkaline
1129 phosphatase, SGOT, SGPT, and bilirubin revealed no differences in the percentage of patients
1130 with marked abnormalities.

1131 **Hallucinations:** In pooled clinical trials of immediate-release paroxetine hydrochloride,
1132 hallucinations were observed in 22 of 9089 patients receiving drug and 4 of 3187 patients
1133 receiving placebo.

1134 **Other Events Observed During the Premarketing Evaluation of PAXIL:** During its
1135 premarketing assessment in major depressive disorder, multiple doses of PAXIL were
1136 administered to 6,145 patients in phase 2 and 3 studies. The conditions and duration of exposure
1137 to PAXIL varied greatly and included (in overlapping categories) open and double-blind studies,
1138 uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose, and titration
1139 studies. During premarketing clinical trials in OCD, panic disorder, social anxiety disorder,
1140 generalized anxiety disorder, and posttraumatic stress disorder, 542, 469, 522, 735, and 676
1141 patients, respectively, received multiple doses of PAXIL. Untoward events associated with this
1142 exposure were recorded by clinical investigators using terminology of their own choosing.
1143 Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals
1144 experiencing adverse events without first grouping similar types of untoward events into a
1145 smaller number of standardized event categories.

1146 In the tabulations that follow, reported adverse events were classified using a standard
1147 COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the
1148 proportion of the 9,089 patients exposed to multiple doses of PAXIL who experienced an event
1149 of the type cited on at least 1 occasion while receiving PAXIL. All reported events are included
1150 except those already listed in Tables 2 to 5, those reported in terms so general as to be
1151 uninformative and those events where a drug cause was remote. It is important to emphasize that
1152 although the events reported occurred during treatment with paroxetine, they were not
1153 necessarily caused by it.

1154 Events are further categorized by body system and listed in order of decreasing frequency
1155 according to the following definitions: Frequent adverse events are those occurring on 1 or more
1156 occasions in at least 1/100 patients (only those not already listed in the tabulated results from

1157 placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in
1158 1/100 to 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients. Events
1159 of major clinical importance are also described in the PRECAUTIONS section.

1160 **Body as a Whole:** *Infrequent:* Allergic reaction, chills, face edema, malaise, neck pain;
1161 *rare:* Adrenergic syndrome, cellulitis, moniliasis, neck rigidity, pelvic pain, peritonitis, sepsis,
1162 ulcer.

1163 **Cardiovascular System:** *Frequent:* Hypertension, tachycardia; *infrequent:* Bradycardia,
1164 hematoma, hypotension, migraine, postural hypotension, syncope; *rare:* Angina pectoris,
1165 arrhythmia nodal, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular
1166 accident, congestive heart failure, heart block, low cardiac output, myocardial infarct, myocardial
1167 ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis,
1168 thrombosis, varicose vein, vascular headache, ventricular extrasystoles.

1169 **Digestive System:** *Infrequent:* Bruxism, colitis, dysphagia, eructation, gastritis,
1170 gastroenteritis, gingivitis, glossitis, increased salivation, liver function tests abnormal, rectal
1171 hemorrhage, ulcerative stomatitis; *rare:* Aphthous stomatitis, bloody diarrhea, bulimia,
1172 cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal
1173 incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, intestinal obstruction,
1174 jaundice, melena, mouth ulceration, peptic ulcer, salivary gland enlargement, sialadenitis,
1175 stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries.

1176 **Endocrine System:** *Rare:* Diabetes mellitus, goiter, hyperthyroidism, hypothyroidism,
1177 thyroiditis.

1178 **Hemic and Lymphatic Systems:** *Infrequent:* Anemia, leukopenia, lymphadenopathy,
1179 purpura; *rare:* Abnormal erythrocytes, basophilia, bleeding time increased, eosinophilia,
1180 hypochromic anemia, iron deficiency anemia, leukocytosis, lymphedema, abnormal
1181 lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia,
1182 thrombocythemia, thrombocytopenia.

1183 **Metabolic and Nutritional:** *Frequent:* Weight gain; *infrequent:* Edema, peripheral edema,
1184 SGOT increased, SGPT increased, thirst, weight loss; *rare:* Alkaline phosphatase increased,
1185 bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, gamma
1186 globulins increased, gout, hypercalcemia, hypercholesteremia, hyperglycemia, hyperkalemia,
1187 hyperphosphatemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, ketosis, lactic
1188 dehydrogenase increased, non-protein nitrogen (NPN) increased.

1189 **Musculoskeletal System:** *Frequent:* Arthralgia; *infrequent:* Arthritis, arthrosis; *rare:*
1190 Bursitis, myositis, osteoporosis, generalized spasm, tenosynovitis, tetany.

1191 **Nervous System:** *Frequent:* Emotional lability, vertigo; *infrequent:* Abnormal thinking,
1192 alcohol abuse, ataxia, dystonia, dyskinesia, euphoria, hallucinations, hostility, hypertonia,
1193 hypesthesia, hypokinesia, incoordination, lack of emotion, libido increased, manic reaction,
1194 neurosis, paralysis, paranoid reaction; *rare:* Abnormal gait, akinesia, antisocial reaction, aphasia,
1195 choreoathetosis, circumoral paresthesias, convulsion, delirium, delusions, diplopia, drug
1196 dependence, dysarthria, extrapyramidal syndrome, fasciculations, grand mal convulsion,

1197 hyperalgesia, hysteria, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy,
1198 nystagmus, peripheral neuritis, psychotic depression, psychosis, reflexes decreased, reflexes
1199 increased, stupor, torticollis, trismus, withdrawal syndrome.

1200 **Respiratory System:** *Infrequent:* Asthma, bronchitis, dyspnea, epistaxis, hyperventilation,
1201 pneumonia, respiratory flu; *rare:* Emphysema, hemoptysis, hiccups, lung fibrosis, pulmonary
1202 edema, sputum increased, stridor, voice alteration.

1203 **Skin and Appendages:** *Frequent:* Pruritus; *infrequent:* Acne, alopecia, contact dermatitis,
1204 dry skin, ecchymosis, eczema, herpes simplex, photosensitivity, urticaria; *rare:* Angioedema,
1205 erythema nodosum, erythema multiforme, exfoliative dermatitis, fungal dermatitis, furunculosis;
1206 herpes zoster, hirsutism, maculopapular rash, seborrhea, skin discoloration, skin hypertrophy,
1207 skin ulcer, sweating decreased, vesiculobullous rash.

1208 **Special Senses:** *Frequent:* Tinnitus; *infrequent:* Abnormality of accommodation,
1209 conjunctivitis, ear pain, eye pain, keratoconjunctivitis, mydriasis, otitis media; *rare:* Amblyopia,
1210 anisocoria, blepharitis, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, eye
1211 hemorrhage, glaucoma, hyperacusis, night blindness, otitis externa, parosmia, photophobia,
1212 ptosis, retinal hemorrhage, taste loss, visual field defect.

1213 **Urogenital System:** *Infrequent:* Amenorrhea, breast pain, cystitis, dysuria, hematuria,
1214 menorrhagia, nocturia, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency,
1215 vaginitis; *rare:* Abortion, breast atrophy, breast enlargement, endometrial disorder, epididymitis,
1216 female lactation, fibrocystic breast, kidney calculus, kidney pain, leukorrhea, mastitis,
1217 metrorrhagia, nephritis, oliguria, salpingitis, urethritis, urinary casts, uterine spasm, urolith,
1218 vaginal hemorrhage, vaginal moniliasis.

1219 **Postmarketing Reports:** Voluntary reports of adverse events in patients taking PAXIL that
1220 have been received since market introduction and not listed above that may have no causal
1221 relationship with the drug include acute pancreatitis, elevated liver function tests (the most
1222 severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated
1223 with severe liver dysfunction), Guillain-Barré syndrome, Stevens-Johnson syndrome, toxic
1224 epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive
1225 of prolactinemia and galactorrhea; extrapyramidal symptoms which have included akathisia,
1226 bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been
1227 associated with concomitant use of pimozide; tremor and trismus; status epilepticus, acute renal
1228 failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic
1229 neuritis, porphyria, restless legs syndrome (RLS), ventricular fibrillation, ventricular tachycardia
1230 (including torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired
1231 hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and
1232 agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura). There has been
1233 a case report of an elevated phenytoin level after 4 weeks of PAXIL and phenytoin
1234 coadministration. There has been a case report of severe hypotension when PAXIL was added to
1235 chronic metoprolol treatment.

1236 **DRUG ABUSE AND DEPENDENCE**

1237 **Controlled Substance Class:** PAXIL is not a controlled substance.

1238 **Physical and Psychologic Dependence:** PAXIL has not been systematically studied in
1239 animals or humans for its potential for abuse, tolerance or physical dependence. While the
1240 clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were
1241 not systematic and it is not possible to predict on the basis of this limited experience the extent to
1242 which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently,
1243 patients should be evaluated carefully for history of drug abuse, and such patients should be
1244 observed closely for signs of misuse or abuse of PAXIL (e.g., development of tolerance,
1245 incrementations of dose, drug-seeking behavior).

1246 **OVERDOSAGE**

1247 **Human Experience:** Since the introduction of PAXIL in the United States, 342 spontaneous
1248 cases of deliberate or accidental overdosage during paroxetine treatment have been reported
1249 worldwide (circa 1999). These include overdoses with paroxetine alone and in combination with
1250 other substances. Of these, 48 cases were fatal and of the fatalities, 17 appeared to involve
1251 paroxetine alone. Eight fatal cases that documented the amount of paroxetine ingested were
1252 generally confounded by the ingestion of other drugs or alcohol or the presence of significant
1253 comorbid conditions. Of 145 non-fatal cases with known outcome, most recovered without
1254 sequelae. The largest known ingestion involved 2,000 mg of paroxetine (33 times the maximum
1255 recommended daily dose) in a patient who recovered.

1256 Commonly reported adverse events associated with paroxetine overdosage include
1257 somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other
1258 notable signs and symptoms observed with overdoses involving paroxetine (alone or with other
1259 substances) include mydriasis, convulsions (including status epilepticus), ventricular
1260 dysrhythmias (including torsade de pointes), hypertension, aggressive reactions, syncope,
1261 hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction
1262 (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin
1263 syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

1264 **Overdosage Management:** No specific antidotes for paroxetine are known. Treatment
1265 should consist of those general measures employed in the management of overdosage with any
1266 drugs effective in the treatment of major depressive disorder.

1267 Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital
1268 signs. General supportive and symptomatic measures are also recommended. Induction of emesis
1269 is not recommended. Due to the large volume of distribution of this drug, forced diuresis,
1270 dialysis, hemoperfusion, or exchange transfusion are unlikely to be of benefit.

1271 A specific caution involves patients who are taking or have recently taken paroxetine who
1272 might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the
1273 parent tricyclic and/or an active metabolite may increase the possibility of clinically significant
1274 sequelae and extend the time needed for close medical observation (see PRECAUTIONS: *Drugs*

1275 *Metabolized by Cytochrome CYP2D6).*

1276 In managing overdosage, consider the possibility of multiple drug involvement. The physician
1277 should consider contacting a poison control center for additional information on the treatment of
1278 any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians'*
1279 *Desk Reference* (PDR).

1280 **DOSAGE AND ADMINISTRATION**

1281 **Major Depressive Disorder: Usual Initial Dosage:** PAXIL should be administered as a
1282 single daily dose with or without food, usually in the morning. The recommended initial dose is
1283 20 mg/day. Patients were dosed in a range of 20 to 50 mg/day in the clinical trials demonstrating
1284 the effectiveness of PAXIL in the treatment of major depressive disorder. As with all drugs
1285 effective in the treatment of major depressive disorder, the full effect may be delayed. Some
1286 patients not responding to a 20-mg dose may benefit from dose increases, in 10-mg/day
1287 increments, up to a maximum of 50 mg/day. Dose changes should occur at intervals of at least
1288 1 week.

1289 **Maintenance Therapy:** There is no body of evidence available to answer the question of
1290 how long the patient treated with PAXIL should remain on it. It is generally agreed that acute
1291 episodes of major depressive disorder require several months or longer of sustained
1292 pharmacologic therapy. Whether the dose needed to induce remission is identical to the dose
1293 needed to maintain and/or sustain euthymia is unknown.

1294 Systematic evaluation of the efficacy of PAXIL has shown that efficacy is maintained for
1295 periods of up to 1 year with doses that averaged about 30 mg.

1296 **Obsessive Compulsive Disorder: Usual Initial Dosage:** PAXIL should be administered
1297 as a single daily dose with or without food, usually in the morning. The recommended dose of
1298 PAXIL in the treatment of OCD is 40 mg daily. Patients should be started on 20 mg/day and the
1299 dose can be increased in 10-mg/day increments. Dose changes should occur at intervals of at
1300 least 1 week. Patients were dosed in a range of 20 to 60 mg/day in the clinical trials
1301 demonstrating the effectiveness of PAXIL in the treatment of OCD. The maximum dosage
1302 should not exceed 60 mg/day.

1303 **Maintenance Therapy:** Long-term maintenance of efficacy was demonstrated in a 6-month
1304 relapse prevention trial. In this trial, patients with OCD assigned to paroxetine demonstrated a
1305 lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY:
1306 Clinical Trials). OCD is a chronic condition, and it is reasonable to consider continuation for a
1307 responding patient. Dosage adjustments should be made to maintain the patient on the lowest
1308 effective dosage, and patients should be periodically reassessed to determine the need for
1309 continued treatment.

1310 **Panic Disorder: Usual Initial Dosage:** PAXIL should be administered as a single daily dose
1311 with or without food, usually in the morning. The target dose of PAXIL in the treatment of panic
1312 disorder is 40 mg/day. Patients should be started on 10 mg/day. Dose changes should occur in
1313 10-mg/day increments and at intervals of at least 1 week. Patients were dosed in a range of 10 to

1314 60 mg/day in the clinical trials demonstrating the effectiveness of PAXIL. The maximum dosage
1315 should not exceed 60 mg/day.

1316 **Maintenance Therapy:** Long-term maintenance of efficacy was demonstrated in a 3-month
1317 relapse prevention trial. In this trial, patients with panic disorder assigned to paroxetine
1318 demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL
1319 PHARMACOLOGY: Clinical Trials). Panic disorder is a chronic condition, and it is reasonable
1320 to consider continuation for a responding patient. Dosage adjustments should be made to
1321 maintain the patient on the lowest effective dosage, and patients should be periodically
1322 reassessed to determine the need for continued treatment.

1323 **Social Anxiety Disorder: Usual Initial Dosage:** PAXIL should be administered as a single
1324 daily dose with or without food, usually in the morning. The recommended and initial dosage is
1325 20 mg/day. In clinical trials the effectiveness of PAXIL was demonstrated in patients dosed in a
1326 range of 20 to 60 mg/day. While the safety of PAXIL has been evaluated in patients with social
1327 anxiety disorder at doses up to 60 mg/day, available information does not suggest any additional
1328 benefit for doses above 20 mg/day (see CLINICAL PHARMACOLOGY: Clinical Trials).

1329 **Maintenance Therapy:** There is no body of evidence available to answer the question of
1330 how long the patient treated with PAXIL should remain on it. Although the efficacy of PAXIL
1331 beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials, social anxiety
1332 disorder is recognized as a chronic condition, and it is reasonable to consider continuation of
1333 treatment for a responding patient. Dosage adjustments should be made to maintain the patient
1334 on the lowest effective dosage, and patients should be periodically reassessed to determine the
1335 need for continued treatment.

1336 **Generalized Anxiety Disorder: Usual Initial Dosage:** PAXIL should be administered as a
1337 single daily dose with or without food, usually in the morning. In clinical trials the effectiveness
1338 of PAXIL was demonstrated in patients dosed in a range of 20 to 50 mg/day. The recommended
1339 starting dosage and the established effective dosage is 20 mg/day. There is not sufficient
1340 evidence to suggest a greater benefit to doses higher than 20 mg/day. Dose changes should occur
1341 in 10 mg/day increments and at intervals of at least 1 week.

1342 **Maintenance Therapy:** Systematic evaluation of continuing PAXIL for periods of up to
1343 24 weeks in patients with Generalized Anxiety Disorder who had responded while taking PAXIL
1344 during an 8-week acute treatment phase has demonstrated a benefit of such maintenance (see
1345 CLINICAL PHARMACOLOGY: Clinical Trials). Nevertheless, patients should be periodically
1346 reassessed to determine the need for maintenance treatment.

1347 **Posttraumatic Stress Disorder: Usual Initial Dosage:** PAXIL should be administered as
1348 a single daily dose with or without food, usually in the morning. The recommended starting
1349 dosage and the established effective dosage is 20 mg/day. In 1 clinical trial, the effectiveness of
1350 PAXIL was demonstrated in patients dosed in a range of 20 to 50 mg/day. However, in a fixed
1351 dose study, there was not sufficient evidence to suggest a greater benefit for a dose of 40 mg/day
1352 compared to 20 mg/day. Dose changes, if indicated, should occur in 10 mg/day increments and at
1353 intervals of at least 1 week.

1354 **Maintenance Therapy:** There is no body of evidence available to answer the question of
1355 how long the patient treated with PAXIL should remain on it. Although the efficacy of PAXIL
1356 beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials, PTSD is
1357 recognized as a chronic condition, and it is reasonable to consider continuation of treatment for a
1358 responding patient. Dosage adjustments should be made to maintain the patient on the lowest
1359 effective dosage, and patients should be periodically reassessed to determine the need for
1360 continued treatment.

1361 **Special Populations: Treatment of Pregnant Women During the Third Trimester:**

1362 Neonates exposed to PAXIL and other SSRIs or SNRIs, late in the third trimester have
1363 developed complications requiring prolonged hospitalization, respiratory support, and tube
1364 feeding (see WARNINGS: Usage in Pregnancy). When treating pregnant women with paroxetine
1365 during the third trimester, the physician should carefully consider the potential risks and benefits
1366 of treatment. The physician may consider tapering paroxetine in the third trimester.

1367 **Dosage for Elderly or Debilitated Patients, and Patients With Severe Renal or
1368 Hepatic Impairment:** The recommended initial dose is 10 mg/day for elderly patients,
1369 debilitated patients, and/or patients with severe renal or hepatic impairment. Increases may be
1370 made if indicated. Dosage should not exceed 40 mg/day.

1371 **Switching Patients to or From a Monoamine Oxidase Inhibitor:** At least 14 days
1372 should elapse between discontinuation of an MAOI and initiation of therapy with PAXIL.
1373 Similarly, at least 14 days should be allowed after stopping PAXIL before starting an MAOI.

1374 **Discontinuation of Treatment With PAXIL:** Symptoms associated with discontinuation of
1375 PAXIL have been reported (see PRECAUTIONS: *Discontinuation of Treatment With PAXIL*).
1376 Patients should be monitored for these symptoms when discontinuing treatment, regardless of the
1377 indication for which PAXIL is being prescribed. A gradual reduction in the dose rather than
1378 abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a
1379 decrease in the dose or upon discontinuation of treatment, then resuming the previously
1380 prescribed dose may be considered. Subsequently, the physician may continue decreasing the
1381 dose but at a more gradual rate.

1382 **NOTE: SHAKE SUSPENSION WELL BEFORE USING.**

1383 **HOW SUPPLIED**

1384 **Tablets:** Film-coated, modified-oval as follows:

1385 10-mg yellow, scored tablets engraved on the front with PAXIL and on the back with 10.

1386 NDC 0029-3210-13 Bottles of 30

1387 20-mg pink, scored tablets engraved on the front with PAXIL and on the back with 20.

1388 NDC 0029-3211-13 Bottles of 30

1389 30-mg blue tablets engraved on the front with PAXIL and on the back with 30.

1390 NDC 0029-3212-13 Bottles of 30

1391 40-mg green tablets engraved on the front with PAXIL and on the back with 40.

1392 NDC 0029-3213-13 Bottles of 30

- 1393 Store tablets between 15° and 30°C (59° and 86°F).
- 1394 **Oral Suspension:** Orange-colored, orange-flavored, 10 mg/5 mL, in 250 mL white bottles.
- 1395 NDC 0029-3215-48
- 1396 Store suspension at or below 25°C (77°F).
- 1397 PAXIL is a registered trademark of GlaxoSmithKline.
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Medication Guide
PAXIL® (PAX-il)
(paroxetine hydrochloride)
Tablets and Oral Suspension

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

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

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

1. Suicidal thoughts or actions:

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

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

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

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

Call your healthcare provider right away if you have any of the following symptoms, or call 911 if an emergency. PAXIL may be associated with these serious side effects:

2. Serotonin Syndrome or Neuroleptic Malignant Syndrome-like reactions. This condition can be life-threatening and may include:

- agitation, hallucinations, coma, or

- other changes in mental status
 - coordination problems or muscle twitching (overactive reflexes)
 - racing heartbeat, high or low blood pressure
 - sweating or fever
 - nausea, vomiting, or diarrhea
 - muscle rigidity
- 3. Severe allergic reactions:**
- trouble breathing
 - swelling of the face, tongue, eyes, or mouth
 - rash, itchy welts (hives), or blisters, alone or with fever or joint pain
- 4. Abnormal bleeding:** PAXIL and other antidepressant medicines may increase your risk of bleeding or bruising, especially if you take the blood thinner warfarin (Coumadin[®], Jantoven[®]), a non-steroidal anti-inflammatory drug (NSAIDs, like ibuprofen or naproxen), or aspirin.
- 5. Seizures or convulsions**
- 6. Manic episodes:**
- greatly increased energy
 - severe trouble sleeping
 - racing thoughts
 - reckless behavior
 - unusually grand ideas
 - excessive happiness or irritability
 - talking more or faster than usual
- 7. Changes in appetite or weight.** Children and adolescents should have height and weight monitored during treatment.
- 8. Low salt (sodium) levels in the blood.** Elderly people may be at greater risk for this. Symptoms may include:
- headache

- weakness or feeling unsteady
- confusion, problems concentrating or thinking, or memory problems

Do not stop PAXIL without first talking to your healthcare provider. Stopping PAXIL too quickly may cause serious symptoms including:

- anxiety, irritability, high or low mood, feeling restless, or changes in sleep habits
- headache, sweating, nausea, dizziness
- electric shock-like sensations, shaking, confusion

What is PAXIL?

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

PAXIL is also used to treat:

- Major Depressive Disorder (MDD)
- Obsessive Compulsive Disorder (OCD)
- Panic Disorder
- Social Anxiety Disorder
- Generalized Anxiety Disorder (GAD)
- Post Traumatic Stress Disorder (PTSD)

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

Who should not take PAXIL?

Do not take PAXIL if you:

- are allergic to paroxetine hydrochloride or any of the ingredients in PAXIL. See the end of this Medication Guide for a complete list of ingredients in PAXIL.

- take a Monoamine Oxidase Inhibitor (MAOI), such as PARNATE[®] (tranylcypromine), NARDIL[®] (phenelzine), or the antibiotic ZYVOX[®] (linezolid). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI.
- Do not take an MAOI within 2 weeks of stopping PAXIL.
- Do not start PAXIL if you stopped taking an MAOI in the last 2 weeks.
- **People who take PAXIL close in time to an MAOI may have serious or even life-threatening side effects. Get medical help right away if you have any of these symptoms:**
 - high fever
 - uncontrolled muscle spasms
 - stiff muscles
 - rapid changes in heart rate or blood pressure
 - confusion
 - loss of consciousness (pass out)
- **take MELLARIL[®] (thioridazine). Do not take MELLARIL[®] together with PAXIL because this can cause serious heart rhythm problems or sudden death.**
- **take the antipsychotic medicine pimozide (ORAP[®]) because this can cause serious heart problems.**

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

Before starting PAXIL, tell your healthcare provider if you:

- **are pregnant, may be pregnant, or plan to become pregnant.** There is a

possibility that PAXIL may harm your unborn baby, including an increased risk of birth defects, particularly heart defects. Other risks may include a serious condition in which there is not enough oxygen in the baby's blood. Your baby may also have certain other symptoms shortly after birth. Premature births have also been reported in some women who used PAXIL during pregnancy.

- **are breastfeeding.** PAXIL passes into your milk. Talk to your healthcare provider about the best way to feed your baby while taking PAXIL.
- are taking certain drugs such as:
 - triptans used to treat migraine headache
 - other antidepressants (SSRIs, SNRIs, tricyclics, or lithium) or antipsychotics
 - drugs that affect serotonin, such as lithium, tramadol, tryptophan, St. John's wort
 - certain drugs used to treat irregular heart beats
 - certain drugs used to treat schizophrenia
 - certain drugs used to treat HIV infection
 - certain drugs that affect the blood, such as warfarin, aspirin, and ibuprofen
 - certain drugs used to treat epilepsy
 - atomoxetine
 - cimetidine
 - fentanyl
 - metoprolol
 - pimozide
 - procyclidine

- tamoxifen
- have liver problems
- have kidney problems
- have heart problems
- have or had seizures or convulsions
- have bipolar disorder or mania
- have low sodium levels in your blood
- have a history of a stroke
- have high blood pressure
- have or had bleeding problems
- have glaucoma (high pressure in the eye)

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. PAXIL and some medicines may interact with each other, may not work as well, or may cause serious side effects.

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

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

How should I take PAXIL?

- Take PAXIL exactly as prescribed. Your healthcare provider may need to change the dose of PAXIL until it is the right dose for you.
- PAXIL may be taken with or without food.
- If you are taking PAXIL Oral Suspension, shake the suspension well before use.

- If you miss a dose of PAXIL, take the missed dose as soon as you remember. If it is almost time for the next dose, skip the missed dose and take your next dose at the regular time. Do not take two doses of PAXIL at the same time.
- If you take too much PAXIL, call your healthcare provider or poison control center right away, or get emergency treatment.
- Do not stop taking PAXIL suddenly without talking to your doctor (unless you have symptoms of a severe allergic reaction). If you need to stop taking PAXIL, your healthcare provider can tell you how to safely stop taking it.

What should I avoid while taking PAXIL?

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

What are possible side effects of PAXIL?

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

Common possible side effects in people who take PAXIL include:

- nausea

- sleepiness
- weakness
- dizziness
- feeling anxious or trouble sleeping
- sexual problems
- sweating
- shaking
- not feeling hungry
- dry mouth
- constipation
- infection
- yawning

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

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

How should I store PAXIL?

- Store PAXIL Tablets at room temperature between 59° and 86°F (15° and 30°C).
- Store PAXIL Oral Suspension at or below 77°F (25°C).
- Keep PAXIL away from light.
- Keep bottle of PAXIL closed tightly.

Keep PAXIL and all medicines out of the reach of children.

General information about PAXIL

Medicines are sometimes prescribed for purposes other than those listed in a

Medication Guide. Do not use PAXIL for a condition for which it was not prescribed. Do not give PAXIL to other people, even if they have the same condition. It may harm them.

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

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

What are the ingredients in PAXIL?

Active ingredient: paroxetine hydrochloride

Inactive ingredients in tablets: dibasic calcium phosphate dihydrate, hypromellose, magnesium stearate, polyethylene glycols, polysorbate 80, sodium starch glycolate, titanium dioxide, and 1 or more of the following: D&C Red No. 30 aluminum lake, D&C Yellow No. 10 aluminum lake, FD&C Blue No. 2 aluminum lake, FD&C Yellow No. 6 aluminum lake.

Inactive ingredients in suspension for oral administration: polacrillin potassium, microcrystalline cellulose, propylene glycol, glycerin, sorbitol, methylparaben, propylparaben, sodium citrate dihydrate, citric acid anhydrous, sodium saccharin, flavorings, FD&C Yellow No. 6 aluminum lake, and simethicone emulsion, USP.

PAXIL is a registered trademark of GlaxoSmithKline. The other brands listed

are trademarks of their respective owners and are not trademarks of GlaxoSmithKline. The makers of these brands are not affiliated with and do not endorse GlaxoSmithKline or

its products.

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

Month Year

PXL:XMG



GlaxoSmithKline
Research Triangle Park, NC 27709

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October 2010

PXL:55PI

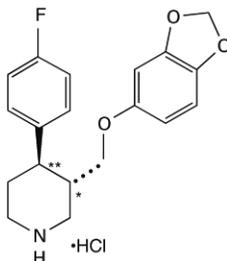
PAXIL CR[®]
(paroxetine hydrochloride)
Controlled-Release Tablets

Suicidality and Antidepressant Drugs

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

DESCRIPTION

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



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

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

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

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

42 **CLINICAL PHARMACOLOGY**

43 **Pharmacodynamics:** The efficacy of paroxetine in the treatment of major depressive
44 disorder, panic disorder, social anxiety disorder, and premenstrual dysphoric disorder (PMDD) is
45 presumed to be linked to potentiation of serotonergic activity in the central nervous system
46 resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT).
47 Studies at clinically relevant doses in humans have demonstrated that paroxetine blocks the
48 uptake of serotonin into human platelets. In vitro studies in animals also suggest that paroxetine
49 is a potent and highly selective inhibitor of neuronal serotonin reuptake and has only very weak
50 effects on norepinephrine and dopamine neuronal reuptake. In vitro radioligand binding studies
51 indicate that paroxetine has little affinity for muscarinic, α_1 -, α_2 -, beta-adrenergic-,
52 dopamine (D_2)-, 5-HT₁-, 5-HT₂-, and histamine (H_1)-receptors; antagonism of muscarinic,
53 histaminergic, and α_1 -adrenergic receptors has been associated with various anticholinergic,
54 sedative, and cardiovascular effects for other psychotropic drugs.

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

57 **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-inf} increased disproportionately with dose (as seen also with immediate-release
72 formulations). Mean C_{max} and AUC_{0-inf} values at these doses were 2.0, 5.5, 9.0, and 12.5 ng/mL,

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

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

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

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

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

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

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

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

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

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

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

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

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

128 **Clinical Trials**

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

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

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

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

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

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

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

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

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

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

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

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

202 **INDICATIONS AND USAGE**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

283 **CONTRAINDICATIONS**

284 PAXIL CR should not be used in patients taking monoamine oxidase inhibitors (MAOIs),
285 including linezolid (an antibiotic which is a reversible non-selective MAOI) and
286 methylthionium chloride (methylene blue), or within 2 weeks of stopping treatment with
287 MAOIs (see WARNINGS).

288 Concomitant use with thioridazine is contraindicated (see WARNINGS and
289 PRECAUTIONS).

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

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

293 **WARNINGS**

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

308 The pooled analyses of placebo-controlled trials in children and adolescents with MDD,
309 obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-
310 term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-

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

319 **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

320
 321 No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but
 322 the number was not sufficient to reach any conclusion about drug effect on suicide.

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

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

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

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

342 If the decision has been made to discontinue treatment, medication should be tapered, as

343 rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with
344 certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION:
345 *Discontinuation of Treatment With PAXIL CR*, for a description of the risks of discontinuation of
346 PAXIL CR).

347 **Families and caregivers of patients being treated with antidepressants for major**
348 **depressive disorder or other indications, both psychiatric and nonpsychiatric, should be**
349 **alerted about the need to monitor patients for the emergence of agitation, irritability,**
350 **unusual changes in behavior, and the other symptoms described above, as well as the**
351 **emergence of suicidality, and to report such symptoms immediately to healthcare**
352 **providers. Such monitoring should include daily observation by families and caregivers.**
353 Prescriptions for PAXIL CR should be written for the smallest quantity of tablets consistent with
354 good patient management, in order to reduce the risk of overdose.

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

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

380 **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions:**
381 **The development of a potentially life-threatening serotonin syndrome or Neuroleptic**
382 **Malignant Syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs**

383 alone, including treatment with PAXIL CR, but particularly with concomitant use of
384 serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin
385 (including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin
386 syndrome symptoms may include mental status changes (e.g., agitation, hallucinations,
387 coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia),
388 neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal
389 symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form
390 can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle
391 rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental
392 status changes. Patients should be monitored for the emergence of serotonin syndrome or
393 NMS-like signs and symptoms.

394 The concomitant use of PAXIL CR with MAOIs intended to treat depression is
395 contraindicated.

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

399 The concomitant use of PAXIL CR with serotonin precursors (such as tryptophan) is
400 not recommended.

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

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

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

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

- 416 • A study based on Swedish national registry data demonstrated that infants exposed to
417 paroxetine during pregnancy (n = 815) had an increased risk of cardiovascular
418 malformations (2% risk in paroxetine-exposed infants) compared to the entire registry
419 population (1% risk), for an odds ratio (OR) of 1.8 (95% confidence interval 1.1 to 2.8). No
420 increase in the risk of overall congenital malformations was seen in the paroxetine-exposed
421 infants. The cardiac malformations in the paroxetine-exposed infants were primarily
422 ventricular septal defects (VSDs) and atrial septal defects (ASDs). Septal defects range in

- 423 severity from those that resolve spontaneously to those which require surgery.
- 424 • A separate retrospective cohort study from the United States (United Healthcare data)
425 evaluated 5,956 infants of mothers dispensed antidepressants during the first trimester
426 (n = 815 for paroxetine). This study showed a trend towards an increased risk for
427 cardiovascular malformations for paroxetine (risk of 1.5%) compared to other
428 antidepressants (risk of 1%), for an OR of 1.5 (95% confidence interval 0.8 to 2.9). Of the
429 12 paroxetine-exposed infants with cardiovascular malformations, 9 had VSDs. This study
430 also suggested an increased risk of overall major congenital malformations including
431 cardiovascular defects for paroxetine (4% risk) compared to other (2% risk) antidepressants
432 (OR 1.8; 95% confidence interval 1.2 to 2.8).
 - 433 • Two large case-control studies using separate databases, each with >9,000 birth defect
434 cases and >4,000 controls, found that maternal use of paroxetine during the first trimester
435 of pregnancy was associated with a 2- to 3-fold increased risk of right ventricular outflow
436 tract obstructions. In one study the OR was 2.5 (95% confidence interval, 1.0 to 6.0, 7
437 exposed infants) and in the other study the OR was 3.3 (95% confidence interval, 1.3 to
438 8.8, 6 exposed infants).

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

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

458 **Animal Findings:** Reproduction studies were performed at doses up to 50 mg/kg/day in rats
459 and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately
460 8 (rat) and 2 (rabbit) times the maximum recommended human dose (MRHD) on an mg/m²
461 basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was
462 an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last

463 trimester of gestation and continued throughout lactation. This effect occurred at a dose of
464 1 mg/kg/day or approximately one-sixth of the MRHD on an mg/m² basis. The no-effect dose for
465 rat pup mortality was not determined. The cause of these deaths is not known.

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

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

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

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

494 PRECAUTIONS

495 **General: Activation of Mania/Hypomania:** During premarketing testing of
496 immediate-release paroxetine hydrochloride, hypomania or mania occurred in approximately
497 1.0% of paroxetine-treated unipolar patients compared to 1.1% of active-control and 0.3% of
498 placebo-treated unipolar patients. In a subset of patients classified as bipolar, the rate of manic
499 episodes was 2.2% for immediate-release paroxetine and 11.6% for the combined active-control
500 groups. Among 1,627 patients with major depressive disorder, panic disorder, social anxiety
501 disorder, or PMDD treated with PAXIL CR in controlled clinical studies, there were no reports

502 of mania or hypomania. As with all drugs effective in the treatment of major depressive disorder,
503 PAXIL CR should be used cautiously in patients with a history of mania.

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

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

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

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

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

538 **Tamoxifen:** Some studies have shown that the efficacy of tamoxifen, as measured by the risk
539 of breast cancer relapse/mortality, may be reduced when co-prescribed with paroxetine as a
540 result of paroxetine's irreversible inhibition of CYP2D6 (see Drug Interactions). However, other
541 studies have failed to demonstrate such a risk. It is uncertain whether the co-administration of

542 paroxetine and tamoxifen has a significant adverse effect on the efficacy of tamoxifen. One study
543 suggests that the risk may increase with longer duration of coadministration. When tamoxifen is
544 used for the treatment or prevention of breast cancer, prescribers should consider using an
545 alternative antidepressant with little or no CYP2D6 inhibition.

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

550 **Hyponatremia:** Hyponatremia may occur as a result of treatment with SSRIs and SNRIs,
551 including PAXIL CR. In many cases, this hyponatremia appears to be the result of the syndrome
552 of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than
553 110 mmol/L have been reported. Elderly patients may be at greater risk of developing
554 hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise
555 volume depleted may be at greater risk (see PRECAUTIONS: Geriatric Use). Discontinuation of
556 PAXIL CR should be considered in patients with symptomatic hyponatremia and appropriate
557 medical intervention should be instituted.

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

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

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

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

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

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

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

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

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

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

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

613 **Clinical Worsening and Suicide Risk:** Patients, their families, and their caregivers
614 should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia,
615 irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness),
616 hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal
617 ideation, especially early during antidepressant treatment and when the dose is adjusted up or
618 down. Families and caregivers of patients should be advised to look for the emergence of such
619 symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be
620 reported to the patient’s prescriber or health professional, especially if they are severe, abrupt in
621 onset, or were not part of the patient’s presenting symptoms. Symptoms such as these may be

622 associated with an increased risk for suicidal thinking and behavior and indicate a need for very
623 close monitoring and possibly changes in the medication.

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

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

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

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

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

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

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

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

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

649 **Drug Interactions: Tryptophan:** As with other serotonin reuptake inhibitors, an interaction
650 between paroxetine and tryptophan may occur when they are coadministered. Adverse
651 experiences, consisting primarily of headache, nausea, sweating, and dizziness, have been
652 reported when tryptophan was administered to patients taking immediate-release paroxetine.
653 Consequently, concomitant use of PAXIL CR with tryptophan is not recommended (see
654 WARNINGS: Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions).

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

656 **Pimozide:** In a controlled study of healthy volunteers, after immediate-release paroxetine
657 hydrochloride was titrated to 60 mg daily, co-administration of a single dose of 2 mg pimozide
658 was associated with mean increases in pimozide AUC of 151% and C_{max} of 62%, compared to
659 pimozide administered alone. The increase in pimozide AUC and C_{max} is due to the CYP2D6
660 inhibitory properties of paroxetine. Due to the narrow therapeutic index of pimozide and its
661 known ability to prolong the QT interval, concomitant use of pimozide and PAXIL CR is

662 contraindicated (see CONTRAINDICATIONS).

663 **Serotonergic Drugs:** Based on the mechanism of action of SNRIs and SSRIs, including
664 paroxetine hydrochloride, and the potential for serotonin syndrome, caution is advised when
665 PAXIL CR is coadministered with other drugs that may affect the serotonergic neurotransmitter
666 systems, such as triptans, lithium, fentanyl, tramadol, or St. John's Wort (see WARNINGS:
667 Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions). The
668 concomitant use of PAXIL CR with MAOIs (including linezolid and methylene blue) is
669 contraindicated (see CONTRAINDICATIONS). The concomitant use of PAXIL CR with other
670 SSRIs, SNRIs or tryptophan is not recommended (see PRECAUTIONS: Drug Interactions,
671 *Tryptophan*).

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

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

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

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

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

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

701 **Phenytoin:** When a single oral 30-mg dose of immediate-release paroxetine was

702 administered at phenytoin steady state (300 mg once daily for 14 days), paroxetine AUC and $T_{1/2}$
703 were reduced (by an average of 50% and 35%, respectively) compared to immediate-release
704 paroxetine administered alone. In a separate study, when a single oral 300-mg dose of phenytoin
705 was administered at paroxetine steady state (30 mg once daily for 14 days), phenytoin AUC was
706 slightly reduced (12% on average) compared to phenytoin administered alone. Since both drugs
707 exhibit nonlinear pharmacokinetics, the above studies may not address the case where the
708 2 drugs are both being chronically dosed. No initial dosage adjustments are considered necessary
709 when PAXIL CR is coadministered with phenytoin; any subsequent adjustments should be
710 guided by clinical effect (see ADVERSE REACTIONS: Postmarketing Reports).

711 **Drugs Metabolized by CYP2D6:** Many drugs, including most drugs effective in the
712 treatment of major depressive disorder (paroxetine, other SSRIs, and many tricyclics), are
713 metabolized by the cytochrome P₄₅₀ isozyme CYP2D6. Like other agents that are metabolized by
714 CYP2D6, paroxetine may significantly inhibit the activity of this isozyme. In most patients
715 (>90%), this CYP2D6 isozyme is saturated early during paroxetine dosing. In 1 study, daily
716 dosing of immediate-release paroxetine (20 mg once daily) under steady-state conditions
717 increased single-dose desipramine (100 mg) C_{max} , AUC, and $T_{1/2}$ by an average of approximately
718 2-, 5-, and 3-fold, respectively. Concomitant use of paroxetine with risperidone, a CYP2D6
719 substrate has also been evaluated. In 1 study, daily dosing of paroxetine 20 mg in patients
720 stabilized on risperidone (4 to 8 mg/day) increased mean plasma concentrations of risperidone
721 approximately 4-fold, decreased 9-hydroxyrisperidone concentrations approximately 10%, and
722 increased concentrations of the active moiety (the sum of risperidone plus 9-hydroxyrisperidone)
723 approximately 1.4-fold. The effect of paroxetine on the pharmacokinetics of atomoxetine has
724 been evaluated when both drugs were at steady state. In healthy volunteers who were extensive
725 metabolizers of CYP2D6, paroxetine 20 mg daily was given in combination with 20 mg
726 atomoxetine every 12 hours. This resulted in increases in steady state atomoxetine AUC values
727 that were 6- to 8-fold greater and in atomoxetine C_{max} values that were 3- to 4-fold greater than
728 when atomoxetine was given alone. Dosage adjustment of atomoxetine may be necessary and it
729 is recommended that atomoxetine be initiated at a reduced dose when given with paroxetine.

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

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

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

741 Tamoxifen is a pro-drug requiring metabolic activation by CYP2D6. Inhibition of CYP2D6

742 by paroxetine may lead to reduced plasma concentrations of an active metabolite (endoxifen) and
743 hence reduced efficacy of tamoxifen (see PRECAUTIONS).

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

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

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

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

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

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

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

780 **Digoxin:** The steady-state pharmacokinetics of paroxetine was not altered when administered
781 with digoxin at steady state. Mean digoxin AUC at steady state decreased by 15% in the

782 presence of paroxetine. Since there is little clinical experience, the concurrent administration of
783 PAXIL CR and digoxin should be undertaken with caution.

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

786 **Procyclidine:** Daily oral dosing of immediate-release paroxetine (30 mg once daily)
787 increased steady-state AUC₀₋₂₄, C_{max}, and C_{min} values of procyclidine (5 mg oral once daily) by
788 35%, 37%, and 67%, respectively, compared to procyclidine alone at steady state. If
789 anticholinergic effects are seen, the dose of procyclidine should be reduced.

790 **Beta-Blockers:** In a study where propranolol (80 mg twice daily) was dosed orally for
791 18 days, the established steady-state plasma concentrations of propranolol were unaltered during
792 coadministration with immediate-release paroxetine (30 mg once daily) for the final 10 days. The
793 effects of propranolol on paroxetine have not been evaluated (see ADVERSE REACTIONS:
794 Postmarketing Reports).

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

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

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

804 **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** Two-year
805 carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and
806 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to approximately 2
807 (mouse) and 3 (rat) times the MRHD on a mg/m² basis. There was a significantly greater number
808 of male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50, and 4/50 for
809 control, low-, middle-, and high-dose groups, respectively) and a significantly increased linear
810 trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats
811 were not affected. Although there was a dose-related increase in the number of tumors in mice,
812 there was no drug-related increase in the number of mice with tumors. The relevance of these
813 findings to humans is unknown.

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

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

821 A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of

822 15 mg/kg/day, which is approximately twice the MRHD on a mg/m² basis. Irreversible lesions
823 occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks.
824 These lesions consisted of vacuolation of epididymal tubular epithelium at 50 mg/kg/day and
825 atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis at
826 25 mg/kg/day (approximately 8 and 4 times the MRHD on a mg/m² basis).

827 **Pregnancy:** Pregnancy Category D. See WARNINGS: Usage in Pregnancy: *Teratogenic* and
828 *Nonteratogenic Effects*.

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

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

832 **Pediatric Use:** Safety and effectiveness in the pediatric population have not been established
833 (see BOX WARNING and WARNINGS: Clinical Worsening and Suicide Risk). Three placebo-
834 controlled trials in 752 pediatric patients with MDD have been conducted with immediate-
835 release PAXIL, and the data were not sufficient to support a claim for use in pediatric patients.
836 Anyone considering the use of PAXIL CR in a child or adolescent must balance the potential
837 risks with the clinical need. Decreased appetite and weight loss have been observed in association
838 with the use of SSRIs. Consequently, regular monitoring of weight and growth should be
839 performed in children and adolescents treated with an SSRI such as PAXIL CR.

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

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

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

855 In worldwide premarketing clinical trials with immediate-release paroxetine hydrochloride,
856 17% of paroxetine-treated patients (approximately 700) were 65 years or older. Pharmacokinetic
857 studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended;
858 there were, however, no overall differences in the adverse event profile between elderly and
859 younger patients, and effectiveness was similar in younger and older patients (see CLINICAL
860 PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

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

862 PAXIL CR was demonstrated to be safe and effective in the treatment of elderly patients (>60
863 years) with major depressive disorder (see CLINICAL PHARMACOLOGY: Clinical Trials and
864 ADVERSE REACTIONS: Table 3.)

865 **ADVERSE REACTIONS**

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

878 **Adverse Findings Observed in Short-Term, Placebo-Controlled Trials With PAXIL 879 CR:**

880 **Adverse Events Associated With Discontinuation of Treatment: *Major Depressive***
881 ***Disorder:*** Ten percent (21/212) of patients treated with PAXIL CR discontinued treatment due
882 to an adverse event in a pool of 2 studies of patients with major depressive disorder. The most
883 common events ($\geq 1\%$) associated with discontinuation and considered to be drug related (i.e.,
884 those events associated with dropout at a rate approximately twice or greater for PAXIL CR
885 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%

886

887 In a placebo-controlled study of elderly patients with major depressive disorder, 13% (13/104)
888 of patients treated with PAXIL CR discontinued due to an adverse event. Events meeting the
889 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%

890

891 **Panic Disorder:** Eleven percent (50/444) of patients treated with PAXIL CR in panic
892 disorder studies discontinued treatment due to an adverse event. Events meeting the above
893 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%

894

895 **Social Anxiety Disorder:** Three percent (5/186) of patients treated with PAXIL CR in the
896 social anxiety disorder study discontinued treatment due to an adverse event. Events meeting the
897 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%

898

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

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

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

910 a. Events considered to be dose dependent are defined as events having an incidence rate with
911 25 mg of PAXIL CR that was at least twice that with 12.5 mg of PAXIL CR (as well as the
912 placebo group).
913

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

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

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

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

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

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

935 of PAXIL CR limited to the 2 weeks prior to the onset of menses over 3 consecutive menstrual
936 cycles, adverse events were evaluated during the first 14 days of each off-drug phase. When the
937 3 off-drug phases were combined, the following adverse events were reported at an incidence of
938 2% or greater for PAXIL CR and were at least twice the rate of that reported for placebo:
939 Infection (5.3% versus 2.5%), depression (2.8% versus 0.8%), insomnia (2.4% versus 0.8%),
940 sinusitis (2.4% versus 0%), and asthenia (2.0% versus 0.8%).

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

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

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

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

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

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

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

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

990 a. Adverse events for which the PAXIL CR reporting incidence was less than or equal to the
991 placebo incidence are not included. These events are nausea and respiratory disorder.
992 b. <1% means greater than zero and less than 1%.
993 c. Based on the number of males.
994 d. Mostly anorgasmia or delayed ejaculation.
995

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

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

- 998 a. Adverse events for which the reporting rate for PAXIL CR was less than or equal to the
 999 placebo rate are not included. These events are: Abnormal dreams, allergic reaction, back
 1000 pain, bronchitis, chest pain, concentration impaired, confusion, cough increased, depression,
 1001 dizziness, dysmenorrhea, dyspepsia, fever, flatulence, headache, increased appetite, infection,
 1002 menstrual disorder, migraine, pain, paresthesia, pharyngitis, respiratory disorder, rhinitis,
 1003 tachycardia, taste perversion, thinking abnormal, urinary tract infection, and vomiting.
- 1004 b. <1% means greater than zero and less than 1%.
- 1005 c. Various physical injuries.
- 1006 d. Mostly flushing.
- 1007 e. Mostly muscle tightness or stiffness.
- 1008 f. Mostly blurred vision.
- 1009 g. Based on the number of male patients.
- 1010 h. Mostly anorgasmia or delayed ejaculation.
- 1011 i. Based on the number of female patients.
- 1012 j. Mostly anorgasmia or difficulty achieving orgasm.

1014 **Table 5. Treatment-Emergent Adverse Effects Occurring in ≥1% of Patients Treated**
 1015 **With PAXIL CR in a Social Anxiety Disorder Study^{a,b}**

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

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

- 1016 a. Adverse events for which the reporting rate for PAXIL CR was less than or equal to the
1017 placebo rate are not included. These events are: Dysmenorrhea, flatulence, gastroenteritis,
1018 hypertonia, infection, pain, pharyngitis, rash, respiratory disorder, rhinitis, and vomiting.
- 1019 b. <1% means greater than zero and less than 1%.
- 1020 c. Various physical injuries.
- 1021 d. Most frequently seasonal allergic symptoms.
- 1022 e. Mostly blurred vision.
- 1023 f. Based on the number of male patients.
- 1024 g. Mostly anorgasmia or delayed ejaculation.
- 1025 h. Based on the number of female patients.
- 1026 i. Mostly anorgasmia or difficulty achieving orgasm.

1027
1028 **Table 6. Treatment-Emergent Adverse Events Occurring in ≥1% of Patients Treated With**
1029 **PAXIL CR in a Pool of 3 Premenstrual Dysphoric Disorder Studies With Continuous**
1030 **Dosing or in 1 Premenstrual Dysphoric Disorder Study With Luteal Phase Dosing^{a,b,c}**

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

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

- 1031 a. Adverse events for which the reporting rate of PAXIL CR was less than or equal to the
1032 placebo rate are not included. These events for continuous dosing are: Abdominal pain, back
1033 pain, pain, trauma, weight gain, myalgia, pharyngitis, respiratory disorder, rhinitis, sinusitis,
1034 pruritis, dysmenorrhea, menstrual disorder, urinary tract infection, and vomiting. The events
1035 for luteal phase dosing are: Allergic reaction, back pain, headache, infection, pain, trauma,
1036 myalgia, anxiety, pharyngitis, respiratory disorder, cystitis, and dysmenorrhea.
- 1037 b. <1% means greater than zero and less than 1%.
- 1038 c. The luteal phase and continuous dosing PMDD trials were not designed for making direct
1039 comparisons between the 2 dosing regimens. Therefore, a comparison between the 2 dosing
1040 regimens of the PMDD trials of incidence rates shown in Table 6 should be avoided.
- 1041 d. Mostly anorgasmia or difficulty achieving orgasm.

1042

1043 **Dose Dependency of Adverse Events:** Table 7 shows results in PMDD trials of
1044 common adverse events, defined as events with an incidence of $\geq 1\%$ with 25 mg of PAXIL CR
1045 that was at least twice that with 12.5 mg of PAXIL CR and with placebo.

1046

1047 **Table 7. Incidence of Common Adverse Events in Placebo, 12.5 mg, and 25 mg of**
1048 **PAXIL CR in a Pool of 3 Fixed-Dose PMDD Trials**

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

1049

1050 A comparison of adverse event rates in a fixed-dose study comparing immediate-release
1051 paroxetine with placebo in the treatment of major depressive disorder revealed a clear dose
1052 dependency for some of the more common adverse events associated with the use of
1053 immediate-release paroxetine.

1054 **Male and Female Sexual Dysfunction With SSRIs:** Although changes in sexual desire,
1055 sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric
1056 disorder, they may also be a consequence of pharmacologic treatment. In particular, some
1057 evidence suggests that SSRIs can cause such untoward sexual experiences.

1058 Reliable estimates of the incidence and severity of untoward experiences involving sexual
1059 desire, performance, and satisfaction are difficult to obtain; however, in part because patients and
1060 physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of
1061 untoward sexual experience and performance cited in product labeling, are likely to
1062 underestimate their actual incidence.

1063 The percentage of patients reporting symptoms of sexual dysfunction in the pool of 2
1064 placebo-controlled trials in nonelderly patients with major depressive disorder, in the pool of 3
1065 placebo-controlled trials in patients with panic disorder, in the placebo-controlled trial in patients
1066 with social anxiety disorder, and in the intermittent dosing and the pool of 3 placebo-controlled
1067 continuous dosing trials in female patients with PMDD are as follows:

1068

	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%

1069

1070 There are no adequate, controlled studies examining sexual dysfunction with paroxetine
1071 treatment.

1072 Paroxetine treatment has been associated with several cases of priapism. In those cases with a
1073 known outcome, patients recovered without sequelae.

1074 While it is difficult to know the precise risk of sexual dysfunction associated with the use of
1075 SSRIs, physicians should routinely inquire about such possible side effects.

1076 **Weight and Vital Sign Changes:** Significant weight loss may be an undesirable result of
1077 treatment with paroxetine for some patients but, on average, patients in controlled trials with
1078 PAXIL CR or the immediate-release formulation, had minimal weight loss (about 1 pound). No
1079 significant changes in vital signs (systolic and diastolic blood pressure, pulse, and temperature)
1080 were observed in patients treated with PAXIL CR, or immediate-release paroxetine
1081 hydrochloride, in controlled clinical trials.

1082 **ECG Changes:** In an analysis of ECGs obtained in 682 patients treated with
1083 immediate-release paroxetine and 415 patients treated with placebo in controlled clinical trials,
1084 no clinically significant changes were seen in the ECGs of either group.

1085 **Liver Function Tests:** In a pool of 2 placebo-controlled clinical trials, patients treated with
1086 PAXIL CR or placebo exhibited abnormal values on liver function tests at comparable rates. In
1087 particular, the controlled-release paroxetine-versus-placebo comparisons for alkaline
1088 phosphatase, SGOT, SGPT, and bilirubin revealed no differences in the percentage of patients
1089 with marked abnormalities.

1090 In a study of elderly patients with major depressive disorder, 3 of 104 patients treated with
1091 PAXIL CR and none of 109 placebo patients experienced liver transaminase elevations of
1092 potential clinical concern.

1093 Two of the patients treated with PAXIL CR dropped out of the study due to abnormal liver
1094 function tests; the third patient experienced normalization of transaminase levels with continued
1095 treatment. Also, in the pool of 3 studies of patients with panic disorder, 4 of 444 patients treated
1096 with PAXIL CR and none of 445 placebo patients experienced liver transaminase elevations of
1097 potential clinical concern. Elevations in all 4 patients decreased substantially after
1098 discontinuation of PAXIL CR. The clinical significance of these findings is unknown.

1099 In placebo-controlled clinical trials with the immediate-release formulation of paroxetine,
1100 patients exhibited abnormal values on liver function tests at no greater rate than that seen in
1101 placebo-treated patients.

1102 **Hallucinations:** In pooled clinical trials of immediate-release paroxetine hydrochloride,
1103 hallucinations were observed in 22 of 9,089 patients receiving drug and in 4 of 3,187 patients
1104 receiving placebo.

1105 **Other Events Observed During the Clinical Development of Paroxetine:** The
1106 following adverse events were reported during the clinical development of PAXIL CR and/or the
1107 clinical development of the immediate-release formulation of paroxetine.

1108 Adverse events for which frequencies are provided below occurred in clinical trials with the
1109 controlled-release formulation of paroxetine. During its premarketing assessment in major
1110 depressive disorder, panic disorder, social anxiety disorder, and PMDD, multiple doses of
1111 PAXIL CR were administered to 1,627 patients in phase 3 double-blind, controlled, outpatient
1112 studies. Untoward events associated with this exposure were recorded by clinical investigators
1113 using terminology of their own choosing. Consequently, it is not possible to provide a
1114 meaningful estimate of the proportion of individuals experiencing adverse events without first
1115 grouping similar types of untoward events into a smaller number of standardized event
1116 categories.

1117 In the tabulations that follow, reported adverse events were classified using a
1118 COSTART-based dictionary. The frequencies presented, therefore, represent the proportion of
1119 the 1,627 patients exposed to PAXIL CR who experienced an event of the type cited on at least 1
1120 occasion while receiving PAXIL CR. All reported events are included except those already listed
1121 in Tables 2 through 7 and those events where a drug cause was remote. If the COSTART term
1122 for an event was so general as to be uninformative, it was deleted or, when possible, replaced
1123 with a more informative term. It is important to emphasize that although the events reported
1124 occurred during treatment with paroxetine, they were not necessarily caused by it.

1125 Events are further categorized by body system and listed in order of decreasing frequency
1126 according to the following definitions: Frequent adverse events are those occurring on 1 or more
1127 occasions in at least 1/100 patients (only those not already listed in the tabulated results from
1128 placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in
1129 1/100 to 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients.

1130 Adverse events for which frequencies are not provided occurred during the premarketing
1131 assessment of immediate-release paroxetine in phase 2 and 3 studies of major depressive
1132 disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized

1133 anxiety disorder, and posttraumatic stress disorder. The conditions and duration of exposure to
1134 immediate-release paroxetine varied greatly and included (in overlapping categories) open and
1135 double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and
1136 fixed-dose and titration studies. Only those events not previously listed for controlled-release
1137 paroxetine are included. The extent to which these events may be associated with PAXIL CR is
1138 unknown.

1139 Events are listed alphabetically within the respective body system. Events of major clinical
1140 importance are also described in the PRECAUTIONS section.

1141 **Body as a Whole:** Infrequent were chills, face edema, fever, flu syndrome, malaise; rare
1142 were abscess, anaphylactoid reaction, anticholinergic syndrome, hypothermia; also observed
1143 were adrenergic syndrome, neck rigidity, sepsis.

1144 **Cardiovascular System:** Infrequent were angina pectoris, bradycardia, hematoma,
1145 hypertension, hypotension, palpitation, postural hypotension, supraventricular tachycardia,
1146 syncope; rare were bundle branch block; also observed were arrhythmia nodal, atrial fibrillation,
1147 cerebrovascular accident, congestive heart failure, low cardiac output, myocardial infarct,
1148 myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles,
1149 thrombophlebitis, thrombosis, vascular headache, ventricular extrasystoles.

1150 **Digestive System:** Infrequent were bruxism, dysphagia, eructation, gastritis,
1151 gastroenteritis, gastroesophageal reflux, gingivitis, hemorrhoids, liver function test abnormal,
1152 melena, pancreatitis, rectal hemorrhage, toothache, ulcerative stomatitis; rare were colitis,
1153 glossitis, gum hyperplasia, hepatosplenomegaly, increased salivation, intestinal obstruction,
1154 peptic ulcer, stomach ulcer, throat tightness; also observed were aphthous stomatitis, bloody
1155 diarrhea, bulimia, cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions,
1156 fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, jaundice, mouth
1157 ulceration, salivary gland enlargement, sialadenitis, stomatitis, tongue discoloration, tongue
1158 edema.

1159 **Endocrine System:** Infrequent were ovarian cyst, testes pain; rare were diabetes mellitus,
1160 hyperthyroidism; also observed were goiter, hypothyroidism, thyroiditis.

1161 **Hemic and Lymphatic System:** Infrequent were anemia, eosinophilia, hypochromic
1162 anemia, leukocytosis, leukopenia, lymphadenopathy, purpura; rare were thrombocytopenia; also
1163 observed were anisocytosis, basophilia, bleeding time increased, lymphedema, lymphocytosis,
1164 lymphopenia, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia.

1165 **Metabolic and Nutritional Disorders:** Infrequent were generalized edema,
1166 hyperglycemia, hypokalemia, peripheral edema, SGOT increased, SGPT increased, thirst; rare
1167 were bilirubinemia, dehydration, hyperkalemia, obesity; also observed were alkaline phosphatase
1168 increased, BUN increased, creatinine phosphokinase increased, gamma globulins increased,
1169 gout, hypercalcemia, hypercholesteremia, hyperphosphatemia, hypocalcemia, hypoglycemia,
1170 hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased.

1171 **Musculoskeletal System:** Infrequent were arthritis, bursitis, tendonitis; rare were
1172 myasthenia, myopathy, myositis; also observed were generalized spasm, osteoporosis,

1173 tenosynovitis, tetany.

1174 **Nervous System:** Frequent were depression; infrequent were amnesia, convulsion,
1175 depersonalization, dystonia, emotional lability, hallucinations, hyperkinesia, hypesthesia,
1176 hypokinesia, incoordination, libido increased, neuralgia, neuropathy, nystagmus, paralysis,
1177 vertigo; rare were ataxia, coma, diplopia, dyskinesia, hostility, paranoid reaction, torticollis,
1178 withdrawal syndrome; also observed were abnormal gait, akathisia, akinesia, aphasia,
1179 choreoathetosis, circumoral paresthesia, delirium, delusions, dysarthria, euphoria, extrapyramidal
1180 syndrome, fasciculations, grand mal convulsion, hyperalgesia, irritability, manic reaction,
1181 manic-depressive reaction, meningitis, myelitis, peripheral neuritis, psychosis, psychotic
1182 depression, reflexes decreased, reflexes increased, stupor, trismus.

1183 **Respiratory System:** Frequent were pharyngitis; infrequent were asthma, dyspnea,
1184 epistaxis, laryngitis, pneumonia; rare were stridor; also observed were dysphonia, emphysema,
1185 hemoptysis, hiccups, hyperventilation, lung fibrosis, pulmonary edema, respiratory flu, sputum
1186 increased.

1187 **Skin and Appendages:** Frequent were rash; infrequent were acne, alopecia, dry skin,
1188 eczema, pruritus, urticaria; rare were exfoliative dermatitis, furunculosis, pustular rash,
1189 seborrhea; also observed were angioedema, ecchymosis, erythema multiforme, erythema
1190 nodosum, hirsutism, maculopapular rash, skin discoloration, skin hypertrophy, skin ulcer,
1191 sweating decreased, vesiculobullous rash.

1192 **Special Senses:** Infrequent were conjunctivitis, earache, keratoconjunctivitis, mydriasis,
1193 photophobia, retinal hemorrhage, tinnitus; rare were blepharitis, visual field defect; also observed
1194 were amblyopia, anisocoria, blurred vision, cataract, conjunctival edema, corneal ulcer, deafness,
1195 exophthalmos, glaucoma, hyperacusis, night blindness, parosmia, ptosis, taste loss.

1196 **Urogenital System:** Frequent were dysmenorrhea^{*}; infrequent were albuminuria,
1197 amenorrhea^{*}, breast pain^{*}, cystitis, dysuria, prostatitis^{*}, urinary retention; rare were breast
1198 enlargement^{*}, breast neoplasm^{*}, female lactation, hematuria, kidney calculus, metrorrhagia^{*},
1199 nephritis, nocturia, pregnancy and puerperal disorders^{*}, salpingitis, urinary incontinence, uterine
1200 fibroids enlarged^{*}; also observed were breast atrophy, ejaculatory disturbance, endometrial
1201 disorder, epididymitis, fibrocystic breast, leukorrhea, mastitis, oliguria, polyuria, pyuria,
1202 urethritis, urinary casts, urinary urgency, urolith, uterine spasm, vaginal hemorrhage.

1203 ^{*}Based on the number of men and women as appropriate.

1204 **Postmarketing Reports:** Voluntary reports of adverse events in patients taking
1205 immediate-release paroxetine hydrochloride that have been received since market introduction
1206 and not listed above that may have no causal relationship with the drug include acute
1207 pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis,
1208 and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré
1209 syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, priapism, syndrome of
1210 inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea;
1211 extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity,
1212 dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of

1213 pimozone; tremor and trismus; status epilepticus, acute renal failure, pulmonary hypertension,
1214 allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, restless legs
1215 syndrome (RLS), ventricular fibrillation, ventricular tachycardia (including torsade de pointes),
1216 thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including
1217 aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic
1218 syndromes (such as Henoch-Schönlein purpura). There has been a case report of an elevated
1219 phenytoin level after 4 weeks of immediate-release paroxetine and phenytoin coadministration.
1220 There has been a case report of severe hypotension when immediate-release paroxetine was
1221 added to chronic metoprolol treatment.

1222 **DRUG ABUSE AND DEPENDENCE**

1223 **Controlled Substance Class:** PAXIL CR is not a controlled substance.

1224 **Physical and Psychologic Dependence:** PAXIL CR has not been systematically studied
1225 in animals or humans for its potential for abuse, tolerance or physical dependence. While the
1226 clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were
1227 not systematic and it is not possible to predict on the basis of this limited experience the extent to
1228 which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently,
1229 patients should be evaluated carefully for history of drug abuse, and such patients should be
1230 observed closely for signs of misuse or abuse of PAXIL CR (e.g., development of tolerance,
1231 incrementations of dose, drug-seeking behavior).

1232 **OVERDOSAGE**

1233 **Human Experience:** Since the introduction of immediate-release paroxetine hydrochloride in
1234 the United States, 342 spontaneous cases of deliberate or accidental overdose during
1235 paroxetine treatment have been reported worldwide (circa 1999). These include overdoses with
1236 paroxetine alone and in combination with other substances. Of these, 48 cases were fatal and of
1237 the fatalities, 17 appeared to involve paroxetine alone. Eight fatal cases that documented the
1238 amount of paroxetine ingested were generally confounded by the ingestion of other drugs or
1239 alcohol or the presence of significant comorbid conditions. Of 145 non-fatal cases with known
1240 outcome, most recovered without sequelae. The largest known ingestion involved 2,000 mg of
1241 paroxetine (33 times the maximum recommended daily dose) in a patient who recovered.

1242 Commonly reported adverse events associated with paroxetine overdose include
1243 somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other
1244 notable signs and symptoms observed with overdoses involving paroxetine (alone or with other
1245 substances) include mydriasis, convulsions (including status epilepticus), ventricular
1246 dysrhythmias (including torsade de pointes), hypertension, aggressive reactions, syncope,
1247 hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction
1248 (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin
1249 syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

1250 **Overdosage Management:** No specific antidotes for paroxetine are known. Treatment
1251 should consist of those general measures employed in the management of overdose with any

1252 drugs effective in the treatment of major depressive disorder.

1253 Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital
1254 signs. General supportive and symptomatic measures are also recommended. Induction of emesis
1255 is not recommended. Due to the large volume of distribution of this drug, forced diuresis,
1256 dialysis, hemoperfusion, or exchange perfusion are unlikely to be of benefit.

1257 A specific caution involves patients taking or recently having taken paroxetine who might
1258 ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the
1259 parent tricyclic and an active metabolite may increase the possibility of clinically significant
1260 sequelae and extend the time needed for close medical observation (see PRECAUTIONS: *Drugs*
1261 *Metabolized by Cytochrome CYP2D6*).

1262 In managing overdose, consider the possibility of multiple-drug involvement. The physician
1263 should consider contacting a poison control center for additional information on the treatment of
1264 any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians'*
1265 *Desk Reference* (PDR).

1266 **DOSAGE AND ADMINISTRATION**

1267 **Major Depressive Disorder: Usual Initial Dosage:** PAXIL CR should be administered as
1268 a single daily dose, usually in the morning, with or without food. The recommended initial dose
1269 is 25 mg/day. Patients were dosed in a range of 25 mg to 62.5 mg/day in the clinical trials
1270 demonstrating the effectiveness of PAXIL CR in the treatment of major depressive disorder. As
1271 with all drugs effective in the treatment of major depressive disorder, the full effect may be
1272 delayed. Some patients not responding to a 25-mg dose may benefit from dose increases, in
1273 12.5-mg/day increments, up to a maximum of 62.5 mg/day. Dose changes should occur at
1274 intervals of at least 1 week.

1275 Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be
1276 swallowed whole.

1277 **Maintenance Therapy:** There is no body of evidence available to answer the question of
1278 how long the patient treated with PAXIL CR should remain on it. It is generally agreed that acute
1279 episodes of major depressive disorder require several months or longer of sustained
1280 pharmacologic therapy. Whether the dose of an antidepressant needed to induce remission is
1281 identical to the dose needed to maintain and/or sustain euthymia is unknown.

1282 Systematic evaluation of the efficacy of immediate-release paroxetine hydrochloride has
1283 shown that efficacy is maintained for periods of up to 1 year with doses that averaged about
1284 30 mg, which corresponds to a 37.5-mg dose of PAXIL CR, based on relative bioavailability
1285 considerations (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

1286 **Panic Disorder: Usual Initial Dosage:** PAXIL CR should be administered as a single daily
1287 dose, usually in the morning. Patients should be started on 12.5 mg/day. Dose changes should
1288 occur in 12.5-mg/day increments and at intervals of at least 1 week. Patients were dosed in a
1289 range of 12.5 to 75 mg/day in the clinical trials demonstrating the effectiveness of PAXIL CR.
1290 The maximum dosage should not exceed 75 mg/day.

1291 Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be
1292 swallowed whole.

1293 **Maintenance Therapy:** Long-term maintenance of efficacy with the immediate-release
1294 formulation of paroxetine was demonstrated in a 3-month relapse prevention trial. In this trial,
1295 patients with panic disorder assigned to immediate-release paroxetine demonstrated a lower
1296 relapse rate compared to patients on placebo. Panic disorder is a chronic condition, and it is
1297 reasonable to consider continuation for a responding patient. Dosage adjustments should be
1298 made to maintain the patient on the lowest effective dosage, and patients should be periodically
1299 reassessed to determine the need for continued treatment.

1300 **Social Anxiety Disorder: Usual Initial Dosage:** PAXIL CR should be administered as a
1301 single daily dose, usually in the morning, with or without food. The recommended initial dose is
1302 12.5 mg/day. Patients were dosed in a range of 12.5 mg to 37.5 mg/day in the clinical trial
1303 demonstrating the effectiveness of PAXIL CR in the treatment of social anxiety disorder. If the
1304 dose is increased, this should occur at intervals of at least 1 week, in increments of 12.5 mg/day,
1305 up to a maximum of 37.5 mg/day.

1306 Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be
1307 swallowed whole.

1308 **Maintenance Therapy:** There is no body of evidence available to answer the question of
1309 how long the patient treated with PAXIL CR should remain on it. Although the efficacy of
1310 PAXIL CR beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials,
1311 social anxiety disorder is recognized as a chronic condition, and it is reasonable to consider
1312 continuation of treatment for a responding patient. Dosage adjustments should be made to
1313 maintain the patient on the lowest effective dosage, and patients should be periodically
1314 reassessed to determine the need for continued treatment.

1315 **Premenstrual Dysphoric Disorder: Usual Initial Dosage:** PAXIL CR should be
1316 administered as a single daily dose, usually in the morning, with or without food. PAXIL CR
1317 may be administered either daily throughout the menstrual cycle or limited to the luteal phase of
1318 the menstrual cycle, depending on physician assessment. The recommended initial dose is
1319 12.5 mg/day. In clinical trials, both 12.5 mg/day and 25 mg/day were shown to be effective.
1320 Dose changes should occur at intervals of at least 1 week.

1321 Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be
1322 swallowed whole.

1323 **Maintenance/Continuation Therapy:** The effectiveness of PAXIL CR for a period
1324 exceeding 3 menstrual cycles has not been systematically evaluated in controlled trials.

1325 However, women commonly report that symptoms worsen with age until relieved by the onset of

1326 menopause. Therefore, it is reasonable to consider continuation of a responding patient. Patients
1327 should be periodically reassessed to determine the need for continued treatment.

1328 **Special Populations: Treatment of Pregnant Women During the Third Trimester:**

1329 Neonates exposed to PAXIL CR and other SSRIs or SNRIs, late in the third trimester have
1330 developed complications requiring prolonged hospitalization, respiratory support, and tube
1331 feeding (see WARNINGS: Usage in Pregnancy). When treating pregnant women with paroxetine
1332 during the third trimester, the physician should carefully consider the potential risks and benefits
1333 of treatment. The physician may consider tapering paroxetine in the third trimester.

1334 **Dosage for Elderly or Debilitated Patients, and Patients With Severe Renal or**
1335 **Hepatic Impairment:** The recommended initial dose of PAXIL CR is 12.5 mg/day for elderly
1336 patients, debilitated patients, and/or patients with severe renal or hepatic impairment. Increases
1337 may be made if indicated. Dosage should not exceed 50 mg/day.

1338 **Switching Patients to or From a Monoamine Oxidase Inhibitor:** At least 14 days
1339 should elapse between discontinuation of an MAOI and initiation of therapy with PAXIL CR.
1340 Similarly, at least 14 days should be allowed after stopping PAXIL CR before starting an MAOI.

1341 **Discontinuation of Treatment With PAXIL CR:** Symptoms associated with discontinuation
1342 of immediate-release paroxetine hydrochloride or PAXIL CR have been reported (see
1343 PRECAUTIONS: *Discontinuation of Treatment with PAXIL CR*). Patients should be monitored
1344 for these symptoms when discontinuing treatment, regardless of the indication for which PAXIL
1345 CR is being prescribed. A gradual reduction in the dose rather than abrupt cessation is
1346 recommended whenever possible. If intolerable symptoms occur following a decrease in the dose
1347 or upon discontinuation of treatment, then resuming the previously prescribed dose may be
1348 considered. Subsequently, the physician may continue decreasing the dose but at a more gradual
1349 rate.

1350 **HOW SUPPLIED**

1351 PAXIL CR is supplied as an enteric film-coated, controlled-release, round tablet, as follows:

1352 12.5-mg yellow tablets

1353 NDC 0029-3206-13 Bottles of 30 (engraved with PAXIL CR and 12.5)

1354 NDC 0029-4606-13 Bottles of 30 (engraved with GSK and 12.5)

1355 25-mg pink tablets

1356 NDC 0029-3207-13 Bottles of 30 (engraved with PAXIL CR and 25)

1357 NDC 0029-4607-13 Bottles of 30 (engraved with GSK and 25)

1358 37.5 mg blue tablets

1359 NDC 0029-3208-13 Bottles of 30 (engraved with PAXIL CR and 37.5)

1360 NDC 0029-4608-13 Bottles of 30 (engraved with GSK and 37.5)

1361 Store at or below 25°C (77°F) [see USP].

1362

1363 PAXIL CR is a registered trademark of GlaxoSmithKline.

1364 GEOMATRIX is a trademark of Jago Pharma, Muttenz, Switzerland.