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PRESCRIBING INFORMATION

PAXIL®
(paroxetine hydrochloride)
Tablets and Oral Suspension

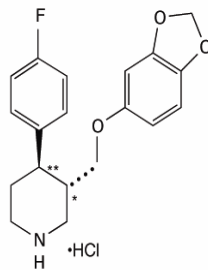
Suicidality and Antidepressant Drugs

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 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 is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

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DESCRIPTION

PAXIL (paroxetine hydrochloride) is an orally administered psychotropic drug. 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:



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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.

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

34 the following: D&C Red No. 30, D&C Yellow No. 10, FD&C Blue No. 2, FD&C Yellow No. 6.
35 **Suspension for Oral Administration:** Each 5 mL of orange-colored, orange-flavored liquid
36 contains paroxetine hydrochloride equivalent to paroxetine, 10 mg. Inactive ingredients consist
37 of polacrillin potassium, microcrystalline cellulose, propylene glycol, glycerin, sorbitol, methyl
38 paraben, propyl paraben, sodium citrate dihydrate, citric acid anhydrate, sodium saccharin,
39 flavorings, FD&C Yellow No. 6, and simethicone emulsion, USP.

40 **CLINICAL PHARMACOLOGY**

41 **Pharmacodynamics:** The efficacy of paroxetine in the treatment of major depressive
42 disorder, social anxiety disorder, obsessive compulsive disorder (OCD), panic disorder (PD),
43 generalized anxiety disorder (GAD), and posttraumatic stress disorder (PTSD) is presumed to be
44 linked to potentiation of serotonergic activity in the central nervous system resulting from
45 inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT). Studies at clinically
46 relevant doses in humans have demonstrated that paroxetine blocks the uptake of serotonin into
47 human platelets. In vitro studies in animals also suggest that paroxetine is a potent and highly
48 selective inhibitor of neuronal serotonin reuptake and has only very weak effects on
49 norepinephrine and dopamine neuronal reuptake. In vitro radioligand binding studies indicate
50 that paroxetine has little affinity for muscarinic, α_1 -, α_2 -, beta-adrenergic-, dopamine
51 (D_2)-, 5-HT₁-, 5-HT₂-, and histamine (H₁)-receptors; antagonism of muscarinic, histaminergic,
52 and α_1 -adrenergic receptors has been associated with various anticholinergic, sedative, and
53 cardiovascular effects for other psychotropic drugs.

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

56 **Pharmacokinetics:** Paroxetine hydrochloride is completely absorbed after oral dosing of a
57 solution of the hydrochloride salt. The mean elimination half-life is approximately 21 hours
58 (CV 32%) after oral dosing of 30 mg tablets of PAXIL daily for 30 days. Paroxetine is
59 extensively metabolized and the metabolites are considered to be inactive. Nonlinearity in
60 pharmacokinetics is observed with increasing doses. Paroxetine metabolism is mediated in part
61 by CYP2D6, and the metabolites are primarily excreted in the urine and to some extent in the
62 feces. Pharmacokinetic behavior of paroxetine has not been evaluated in subjects who are
63 deficient in CYP2D6 (poor metabolizers).

64 **Absorption and Distribution:** Paroxetine is equally bioavailable from the oral suspension
65 and tablet.

66 Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the
67 hydrochloride salt. In a study in which normal male subjects (n = 15) received 30 mg tablets
68 daily for 30 days, steady-state paroxetine concentrations were achieved by approximately
69 10 days for most subjects, although it may take substantially longer in an occasional patient. At
70 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.
71 (CV 10%), 30.7 ng/mL (CV 67%), and 21.0 hours (CV 32%), respectively. The steady-state C_{max}
72 and C_{min} values were about 6 and 14 times what would be predicted from single-dose studies.

73 Steady-state drug exposure based on AUC_{0-24} was about 8 times greater than would have been
74 predicted from single-dose data in these subjects. The excess accumulation is a consequence of
75 the fact that 1 of the enzymes that metabolizes paroxetine is readily saturable.

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

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

82 Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/mL and
83 400 ng/mL, respectively. Under clinical conditions, paroxetine concentrations would normally be
84 less than 400 ng/mL. Paroxetine does not alter the in vitro protein binding of phenytoin or
85 warfarin.

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

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

102 Approximately 64% of a 30-mg oral solution dose of paroxetine was excreted in the urine
103 with 2% as the parent compound and 62% as metabolites over a 10-day post-dosing period.
104 About 36% was excreted in the feces (probably via the bile), mostly as metabolites and less than
105 1% as the parent compound over the 10-day post-dosing period.

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

112 The initial dosage should therefore be reduced in patients with severe renal or hepatic

113 impairment, and upward titration, if necessary, should be at increased intervals (see DOSAGE
114 AND ADMINISTRATION).

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

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

123 **Clinical Trials**

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

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

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

151 The following table provides the outcome classification by treatment group on Global

152 Improvement items of the Clinical Global Impression (CGI) scale for Study 1.

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| 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% |

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

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

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

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

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

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

180 In both Studies 2 and 3, the mean paroxetine dose for completers at endpoint was
181 approximately 40 mg/day of paroxetine.

182 Long-term maintenance effects of PAXIL in panic disorder were demonstrated in an
183 extension to Study 1. Patients who were responders during the 10-week double-blind phase and

184 during a 3-month double-blind extension phase were randomized to either paroxetine (10, 20, or
185 40 mg/day) or placebo in a 3-month double-blind relapse prevention phase. Patients randomized
186 to paroxetine were significantly less likely to relapse than comparably treated patients who were
187 randomized to placebo.

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

190 **Social Anxiety Disorder:** The effectiveness of PAXIL in the treatment of social anxiety
191 disorder was demonstrated in three 12-week, multicenter, placebo-controlled studies (Studies 1,
192 2, and 3) of adult outpatients with social anxiety disorder (DSM-IV). In these studies, the
193 effectiveness of PAXIL compared to placebo was evaluated on the basis of (1) the proportion of
194 responders, as defined by a Clinical Global Impression (CGI) Improvement score of 1 (very
195 much improved) or 2 (much improved), and (2) change from baseline in the Liebowitz Social
196 Anxiety Scale (LSAS).

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

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

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

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

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

219 Study 2 was a flexible-dose study comparing paroxetine (20 mg to 50 mg daily) and placebo.
220 PAXIL demonstrated statistically significant superiority over placebo on the Hamilton Rating
221 Scale for Anxiety (HAM-A) total score. A third study, also flexible-dose comparing paroxetine
222 (20 mg to 50 mg daily), did not demonstrate statistically significant superiority of PAXIL over
223 placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score, the primary outcome.

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

226 In a longer-term trial, 566 patients meeting DSM-IV criteria for Generalized Anxiety
227 Disorder, who had responded during a single-blind, 8-week acute treatment phase with 20 to
228 50 mg/day of PAXIL, were randomized to continuation of PAXIL at their same dose, or to
229 placebo, for up to 24 weeks of observation for relapse. Response during the single-blind phase
230 was defined by having a decrease of ≥ 2 points compared to baseline on the CGI-Severity of
231 Illness scale, to a score of ≤ 3 . Relapse during the double-blind phase was defined as an increase
232 of ≥ 2 points compared to baseline on the CGI-Severity of Illness scale to a score of ≥ 4 , or
233 withdrawal due to lack of efficacy. Patients receiving continued PAXIL experienced a
234 significantly lower relapse rate over the subsequent 24 weeks compared to those receiving
235 placebo.

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

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

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

257 A third study, also a flexible-dose study comparing paroxetine (20 to 50 mg daily) to placebo,
258 demonstrated PAXIL to be significantly superior to placebo on change from baseline for CAPS-
259 2 total score, but not on proportion of responders on the CGI-I.

260 The majority of patients in these trials were women (68% women: 377 out of 551 subjects in
261 Study 1 and 66% women: 202 out of 303 subjects in Study 2). Subgroup analyses did not
262 indicate differences in treatment outcomes as a function of gender. There were an insufficient
263 number of patients who were 65 years and older or were non-Caucasian to conduct subgroup

264 analyses on the basis of age or race, respectively.

265 **INDICATIONS AND USAGE**

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

268 The efficacy of PAXIL in the treatment of a major depressive episode was established in
269 6-week controlled trials of outpatients whose diagnoses corresponded most closely to the
270 DSM-III category of major depressive disorder (see CLINICAL PHARMACOLOGY—Clinical
271 Trials). A major depressive episode implies a prominent and relatively persistent depressed or
272 dysphoric mood that usually interferes with daily functioning (nearly every day for at least
273 2 weeks); it should include at least 4 of the following 8 symptoms: Change in appetite, change in
274 sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in
275 sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired
276 concentration, and a suicide attempt or suicidal ideation.

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

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

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

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

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

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

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

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

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

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

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

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

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

337 **Generalized Anxiety Disorder:** PAXIL is indicated for the treatment of Generalized Anxiety
338 Disorder (GAD), as defined in DSM-IV. Anxiety or tension associated with the stress of
339 everyday life usually does not require treatment with an anxiolytic.

340 The efficacy of PAXIL in the treatment of GAD was established in two 8-week
341 placebo-controlled trials in adults with GAD. PAXIL has not been studied in children or
342 adolescents with Generalized Anxiety Disorder (see CLINICAL PHARMACOLOGY—Clinical

343 Trials).

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

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

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

358 The efficacy of PAXIL in the treatment of PTSD was established in two 12-week placebo-
359 controlled trials in adults with PTSD (DSM-IV) (see CLINICAL PHARMACOLOGY—Clinical
360 Trials).

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

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

378 **CONTRAINDICATIONS**

379 Concomitant use in patients taking either monoamine oxidase inhibitors (MAOIs) or
380 thioridazine is contraindicated (see WARNINGS and PRECAUTIONS).

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

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

384 **WARNINGS**

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

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

410

411 **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 |

412

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

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

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

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

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

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

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

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

451 **Potential for Interaction With Monoamine Oxidase Inhibitors: In patients receiving**
452 **another serotonin reuptake inhibitor drug in combination with a monoamine oxidase**

453 inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including
454 hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of
455 vital signs, and mental status changes that include extreme agitation progressing to
456 delirium and coma. These reactions have also been reported in patients who have recently
457 discontinued that drug and have been started on an MAOI. Some cases presented with
458 features resembling neuroleptic malignant syndrome. While there are no human data
459 showing such an interaction with PAXIL, limited animal data on the effects of combined
460 use of paroxetine and MAOIs suggest that these drugs may act synergistically to elevate
461 blood pressure and evoke behavioral excitation. Therefore, it is recommended that PAXIL
462 not be used in combination with an MAOI, or within 14 days of discontinuing treatment
463 with an MAOI. At least 2 weeks should be allowed after stopping PAXIL before starting an
464 MAOI.

465 **Serotonin Syndrome:** The development of a potentially life-threatening serotonin
466 syndrome may occur with SNRIs and SSRIs, including PAXIL, particularly with
467 concomitant use of serotonergic drugs (including triptans) and with drugs which impair
468 metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include
469 mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g.,
470 tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g.,
471 hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting,
472 diarrhea).

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

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

479 The concomitant use of PAXIL with serotonin precursors (such as tryptophan) is not
480 recommended (see PRECAUTIONS—Drug Interactions).

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

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

489 **Usage in Pregnancy: *Teratogenic Effects:*** Epidemiological studies have shown that
490 infants born to women who had first trimester paroxetine exposure had an increased risk of
491 cardiovascular malformations, primarily ventricular and atrial septal defects (VSDs and ASDs).
492 In general, septal defects range from those that are symptomatic and may require surgery to those

493 that are asymptomatic and may resolve spontaneously. If a patient becomes pregnant while
494 taking paroxetine, she should be advised of the potential harm to the fetus. Unless the benefits of
495 paroxetine to the mother justify continuing treatment, consideration should be given to either
496 discontinuing paroxetine therapy or switching to another antidepressant (see PRECAUTIONS—
497 Discontinuation of Treatment with PAXIL). For women who intend to become pregnant or are in
498 their first trimester of pregnancy, paroxetine should only be initiated after consideration of the
499 other available treatment options.

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

508 A separate retrospective cohort study using US United Healthcare data evaluated 5,956 infants
509 of mothers dispensed paroxetine or other antidepressants during the first trimester (n = 815 for
510 paroxetine). This study showed a trend towards an increased risk for cardiovascular
511 malformations for paroxetine compared to other antidepressants (OR 1.5; 95% confidence
512 interval 0.8-2.9). The prevalence of cardiovascular malformations following first trimester
513 dispensing was 1.5% for paroxetine vs. 1% for other antidepressants. Nine out of 12 infants with
514 cardiovascular malformations whose mothers were dispensed paroxetine in the first trimester had
515 VSDs. This study also suggested an increased risk of overall major congenital malformations
516 (inclusive of the cardiovascular defects) for paroxetine compared to other antidepressants (OR
517 1.8; 95% confidence interval 1.2-2.8). The prevalence of all congenital malformations following
518 first trimester exposure was 4% for paroxetine vs. 2% for other antidepressants.

519 **Animal Findings:** Reproduction studies were performed at doses up to 50 mg/kg/day in rats
520 and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately
521 8 (rat) and 2 (rabbit) times the MRHD on an mg/m² basis. These studies have revealed no
522 evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the
523 first 4 days of lactation when dosing occurred during the last trimester of gestation and continued
524 throughout lactation. This effect occurred at a dose of 1 mg/kg/day or approximately one-sixth of
525 the MRHD on an mg/m² basis. The no-effect dose for rat pup mortality was not determined. The
526 cause of these deaths is not known.

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

533 constant crying. These features are consistent with either a direct toxic effect of SSRIs and
534 SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the
535 clinical picture is consistent with serotonin syndrome (see WARNINGS—Potential for
536 Interaction With Monoamine Oxidase Inhibitors).

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

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

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

555 **PRECAUTIONS**

556 **General: Activation of Mania/Hypomania:** During premarketing testing, hypomania or
557 mania occurred in approximately 1.0% of unipolar patients treated with PAXIL compared to
558 1.1% of active-control and 0.3% of placebo-treated unipolar patients. In a subset of patients
559 classified as bipolar, the rate of manic episodes was 2.2% for PAXIL and 11.6% for the
560 combined active-control groups. As with all drugs effective in the treatment of major depressive
561 disorder, PAXIL should be used cautiously in patients with a history of mania.

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

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

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

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

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

588 See also PRECAUTIONS—Pediatric Use, for adverse events reported upon discontinuation
589 of treatment with PAXIL in pediatric patients.

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

594 **Hyponatremia:** Several cases of hyponatremia have been reported. The hyponatremia
595 appeared to be reversible when PAXIL was discontinued. The majority of these occurrences
596 have been in elderly individuals, some in patients taking diuretics or who were otherwise volume
597 depleted.

598 **Abnormal Bleeding:** Published case reports have documented the occurrence of bleeding
599 episodes in patients treated with psychotropic agents that interfere with serotonin reuptake.
600 Subsequent epidemiological studies, both of the case-control and cohort design, have
601 demonstrated an association between use of psychotropic drugs that interfere with serotonin
602 reuptake and the occurrence of upper gastrointestinal bleeding. In 2 studies, concurrent use of a
603 nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (see
604 Drug Interactions). Although these studies focused on upper gastrointestinal bleeding, there is
605 reason to believe that bleeding at other sites may be similarly potentiated. Patients should be
606 cautioned regarding the risk of bleeding associated with the concomitant use of paroxetine with
607 NSAIDs, aspirin, or other drugs that affect coagulation.

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

611 As with other SSRIs, mydriasis has been infrequently reported in premarketing studies with

612 PAXIL. A few cases of acute angle closure glaucoma associated with paroxetine therapy have
613 been reported in the literature. As mydriasis can cause acute angle closure in patients with
614 narrow angle glaucoma, caution should be used when PAXIL is prescribed for patients with
615 narrow angle glaucoma.

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

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

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

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

630 Prescribers or other health professionals should inform patients, their families, and their
631 caregivers about the benefits and risks associated with treatment with PAXIL and should counsel
632 them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines,
633 Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions" is available
634 for PAXIL. The prescriber or health professional should instruct patients, their families, and their
635 caregivers to read the Medication Guide and should assist them in understanding its contents.
636 Patients should be given the opportunity to discuss the contents of the Medication Guide and to
637 obtain answers to any questions they may have. The complete text of the Medication Guide is
638 reprinted at the end of this document.

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

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

652 **Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.):** Patients
653 should be cautioned about the concomitant use of paroxetine and NSAIDs, aspirin, or other drugs
654 that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin
655 reuptake and these agents has been associated with an increased risk of bleeding.

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

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

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

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

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

671 **Nursing:** Patients should be advised to notify their physician if they are breast-feeding an
672 infant (see PRECAUTIONS—Nursing Mothers).

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

674 **Drug Interactions: Tryptophan:** As with other serotonin reuptake inhibitors, an interaction
675 between paroxetine and tryptophan may occur when they are coadministered. Adverse
676 experiences, consisting primarily of headache, nausea, sweating, and dizziness, have been
677 reported when tryptophan was administered to patients taking PAXIL. Consequently,
678 concomitant use of PAXIL with tryptophan is not recommended (see WARNINGS—Serotonin
679 Syndrome).

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

681 **Pimozide:** In a controlled study of healthy volunteers, after PAXIL was titrated to 60 mg
682 daily, co-administration of a single dose of 2 mg pimozide was associated with mean increases in
683 pimozide AUC of 151% and C_{max} of 62%, compared to pimozide administered alone. Due to the
684 narrow therapeutic index of pimozide and its known ability to prolong the QT interval,
685 concomitant use of pimozide and PAXIL is contraindicated (see CONTRAINDICATIONS).

686 **Serotonergic Drugs:** Based on the mechanism of action of SNRIs and SSRIs, including
687 paroxetine hydrochloride, and the potential for serotonin syndrome, caution is advised when
688 PAXIL is coadministered with other drugs that may affect the serotonergic neurotransmitter
689 systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI),
690 lithium, tramadol, or St. John's Wort (see WARNINGS—Serotonin Syndrome). The concomitant
691 use of PAXIL with other SSRIs, SNRIs or tryptophan is not recommended (see

692 PRECAUTIONS—Drug Interactions, *Tryptophan*).

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

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

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

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

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

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

721 **Phenytoin:** When a single oral 30-mg dose of PAXIL was administered at phenytoin steady
722 state (300 mg once daily for 14 days), paroxetine AUC and T_{1/2} were reduced (by an average of
723 50% and 35%, respectively) compared to PAXIL administered alone. In a separate study, when a
724 single oral 300-mg dose of phenytoin was administered at paroxetine steady state (30 mg once
725 daily for 14 days), phenytoin AUC was slightly reduced (12% on average) compared to
726 phenytoin administered alone. Since both drugs exhibit nonlinear pharmacokinetics, the above
727 studies may not address the case where the 2 drugs are both being chronically dosed. No initial
728 dosage adjustments are considered necessary when these drugs are coadministered; any
729 subsequent adjustments should be guided by clinical effect (see ADVERSE REACTIONS—
730 Postmarketing Reports).

731 **Drugs Metabolized by CYP2D6:** Many drugs, including most drugs effective in the

732 treatment of major depressive disorder (paroxetine, other SSRIs and many tricyclics), are
733 metabolized by the cytochrome P₄₅₀ isozyme CYP2D6. Like other agents that are metabolized by
734 CYP2D6, paroxetine may significantly inhibit the activity of this isozyme. In most patients
735 (>90%), this CYP2D6 isozyme is saturated early during dosing with PAXIL. In 1 study, daily
736 dosing of PAXIL (20 mg once daily) under steady-state conditions increased single dose
737 desipramine (100 mg) C_{max}, AUC, and T_{1/2} by an average of approximately 2-, 5-, and 3-fold,
738 respectively. Concomitant use of paroxetine with risperidone, a CYP2D6 substrate has also been
739 evaluated. In 1 study, daily dosing of paroxetine 20 mg in patients stabilized on risperidone (4 to
740 8 mg/day) increased mean plasma concentrations of risperidone approximately 4-fold, decreased
741 9-hydroxyrisperidone concentrations approximately 10%, and increased concentrations of the
742 active moiety (the sum of risperidone plus 9-hydroxyrisperidone) approximately 1.4-fold. The
743 effect of paroxetine on the pharmacokinetics of atomoxetine has been evaluated when both drugs
744 were at steady state. In healthy volunteers who were extensive metabolizers of CYP2D6,
745 paroxetine 20 mg daily was given in combination with 20 mg atomoxetine every 12 hours. This
746 resulted in increases in steady state atomoxetine AUC values that were 6- to 8-fold greater and in
747 atomoxetine C_{max} values that were 3- to 4-fold greater than when atomoxetine was given alone.
748 Dosage adjustment of atomoxetine may be necessary and it is recommended that atomoxetine be
749 initiated at a reduced dose when it is given with paroxetine.

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

753 Therefore, coadministration of PAXIL with other drugs that are metabolized by this isozyme,
754 including certain drugs effective in the treatment of major depressive disorder (e.g., nortriptyline,
755 amitriptyline, imipramine, desipramine, and fluoxetine), phenothiazines, risperidone, and Type
756 1C antiarrhythmics (e.g., propafenone, flecainide, and encainide), or that inhibit this enzyme
757 (e.g., quinidine), should be approached with caution.

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

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

764 **Drugs Metabolized by Cytochrome CYP3A4:** An in vivo interaction study involving
765 the coadministration under steady-state conditions of paroxetine and terfenadine, a substrate for
766 cytochrome CYP3A4, revealed no effect of paroxetine on terfenadine pharmacokinetics. In
767 addition, in vitro studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be
768 at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several
769 substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam, and
770 cyclosporine. Based on the assumption that the relationship between paroxetine's in vitro K_i and
771 its lack of effect on terfenadine's in vivo clearance predicts its effect on other CYP3A4

772 substrates, paroxetine's extent of inhibition of CYP3A4 activity is not likely to be of clinical
773 significance.

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

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

784 **Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.):**
785 Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of
786 the case-control and cohort design that have demonstrated an association between use of
787 psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper
788 gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentiated
789 the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently
790 with paroxetine.

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

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

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

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

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

806 **Beta-Blockers:** In a study where propranolol (80 mg twice daily) was dosed orally for
807 18 days, the established steady-state plasma concentrations of propranolol were unaltered during
808 coadministration with PAXIL (30 mg once daily) for the final 10 days. The effects of
809 propranolol on paroxetine have not been evaluated (see ADVERSE REACTIONS—
810 Postmarketing Reports).

811 **Theophylline:** Reports of elevated theophylline levels associated with treatment with

812 PAXIL have been reported. While this interaction has not been formally studied, it is
813 recommended that theophylline levels be monitored when these drugs are concurrently
814 administered.

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

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

820 **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** Two-year
821 carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and
822 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to 2.4 (mouse) and
823 3.9 (rat) times the maximum recommended human dose (MRHD) for major depressive disorder,
824 social anxiety disorder, GAD, and PTSD on a mg/m² basis. Because the MRHD for major
825 depressive disorder is slightly less than that for OCD (50 mg versus 60 mg), the doses used in
826 these carcinogenicity studies were only 2.0 (mouse) and 3.2 (rat) times the MRHD for OCD.
827 There was a significantly greater number of male rats in the high-dose group with reticulum cell
828 sarcomas (1/100, 0/50, 0/50, and 4/50 for control, low-, middle-, and high-dose groups,
829 respectively) and a significantly increased linear trend across dose groups for the occurrence of
830 lymphoreticular tumors in male rats. Female rats were not affected. Although there was a
831 dose-related increase in the number of tumors in mice, there was no drug-related increase in the
832 number of mice with tumors. The relevance of these findings to humans is unknown.

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

837 **Impairment of Fertility:** A reduced pregnancy rate was found in reproduction studies in
838 rats at a dose of paroxetine of 15 mg/kg/day, which is 2.9 times the MRHD for major depressive
839 disorder, social anxiety disorder, GAD, and PTSD or 2.4 times the MRHD for OCD on a mg/m²
840 basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity
841 studies for 2 to 52 weeks. These lesions consisted of vacuolation of epididymal tubular
842 epithelium at 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with
843 arrested spermatogenesis at 25 mg/kg/day (9.8 and 4.9 times the MRHD for major depressive
844 disorder, social anxiety disorder, and GAD; 8.2 and 4.1 times the MRHD for OCD and PD on a
845 mg/m² basis).

846 **Pregnancy:** Pregnancy Category D. See WARNINGS—Usage in Pregnancy: *Teratogenic and*
847 *Nonteratogenic Effects.*

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

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

851 **Pediatric Use:** Safety and effectiveness in the pediatric population have not been established

852 (see BOX WARNING and WARNINGS—Clinical Worsening and Suicide Risk). Three
853 placebo-controlled trials in 752 pediatric patients with MDD have been conducted with PAXIL,
854 and the data were not sufficient to support a claim for use in pediatric patients. Anyone
855 considering the use of PAXIL in a child or adolescent must balance the potential risks with the
856 clinical need.

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

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

867 **Geriatric Use:** In worldwide premarketing clinical trials with PAXIL, 17% of patients treated
868 with PAXIL (approximately 700) were 65 years of age or older. Pharmacokinetic studies
869 revealed a decreased clearance in the elderly, and a lower starting dose is recommended; there
870 were, however, no overall differences in the adverse event profile between elderly and younger
871 patients, and effectiveness was similar in younger and older patients (see CLINICAL
872 PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

873 **ADVERSE REACTIONS**

874 **Associated With Discontinuation of Treatment:** Twenty percent (1,199/6,145) of patients
875 treated with PAXIL in worldwide clinical trials in major depressive disorder and 16.1%
876 (84/522), 11.8% (64/542), 9.4% (44/469), 10.7% (79/735), and 11.7% (79/676) of patients
877 treated with PAXIL in worldwide trials in social anxiety disorder, OCD, panic disorder, GAD,
878 and PTSD, respectively, discontinued treatment due to an adverse event. The most common
879 events ($\geq 1\%$) associated with discontinuation and considered to be drug related (i.e., those events
880 associated with dropout at a rate approximately twice or greater for PAXIL compared to placebo)
881 included the following:

882

| | 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 ¹ | 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 ¹ | — | | 1.5% | 0% | | | | | | | — | — |
| Libido Decreased | | | | | | | 1.0% | 0% | | | — | — |

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

885 1. Incidence corrected for gender.

886

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

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

896 **Panic Disorder:** The most commonly observed adverse events associated with the use of
897 paroxetine (incidence of 5% or greater and incidence for PAXIL at least twice that for placebo,
898 derived from Table 3) were: Asthenia, sweating, decreased appetite, libido decreased, tremor,
899 abnormal ejaculation, female genital disorders, and impotence.

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

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

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

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

923 **Major Depressive Disorder:** Table 2 enumerates adverse events that occurred at an
924 incidence of 1% or more among paroxetine-treated patients who participated in short-term
925 (6-week) placebo-controlled trials in which patients were dosed in a range of 20 mg to
926 50 mg/day. Reported adverse events were classified using a standard COSTART-based
927 Dictionary terminology.

928

929 **Table 2. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled**
930 **Clinical Trials for Major Depressive Disorder¹**

| 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 ² | 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 ^{3,4} | 13% | 0% |
| | Other Male Genital Disorders ^{3,5} | 10% | 0% |
| | Urinary Frequency | 3% | 1% |
| | Urination Disorder ⁶ | 3% | 0% |
| | Female Genital Disorders ^{3,7} | 2% | 0% |

- 931 1. Events reported by at least 1% of patients treated with PAXIL are included, except the
932 following events which had an incidence on placebo \geq PAXIL: Abdominal pain, agitation,
933 back pain, chest pain, CNS stimulation, fever, increased appetite, myoclonus, pharyngitis,
934 postural hypotension, respiratory disorder (includes mostly “cold symptoms” or “URI”),
935 trauma, and vomiting.
936 2. Includes mostly “lump in throat” and “tightness in throat.”

- 937 3. Percentage corrected for gender.
 938 4. Mostly “ejaculatory delay.”
 939 5. Includes “anorgasmia,” “erectile difficulties,” “delayed ejaculation/orgasm,” and “sexual
 940 dysfunction,” and “impotence.”
 941 6. Includes mostly “difficulty with micturition” and “urinary hesitancy.”
 942 7. Includes mostly “anorgasmia” and “difficulty reaching climax/orgasm.”
 943

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

944 Table 3 enumerates adverse events that occurred at a frequency of 2% or more among OCD
 945 patients on PAXIL who participated in placebo-controlled trials of 12-weeks duration in which
 946 patients were dosed in a range of 20 mg to 60 mg/day or among patients with panic disorder on
 947 PAXIL who participated in placebo-controlled trials of 10- to 12-weeks duration in which
 948 patients were dosed in a range of 10 mg to 60 mg/day or among patients with social anxiety
 949 disorder on PAXIL who participated in placebo-controlled trials of 12-weeks duration in which
 950 patients were dosed in a range of 20 mg to 50 mg/day.
 951
 952

953 **Table 3. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled**
 954 **Clinical Trials for Obsessive Compulsive Disorder, Panic Disorder, and Social Anxiety**
 955 **Disorder¹**

| 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 Appetite | 4% | 3% | 2% | 1% | — | — |

| | | Obsessive Compulsive Disorder | | Panic Disorder | | Social Anxiety Disorder | |
|-------------------|--------------------------------------|-------------------------------|-----|----------------|-----|-------------------------|-----|
| | | | | | | | |
| | 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 ² | 23% | 1% | 21% | 1% | 28% | 1% |
| | Dysmenorrhea | — | — | — | — | 5% | 4% |
| | Female Genital Disorder ² | 3% | 0% | 9% | 1% | 9% | 1% |
| | Impotence ² | 8% | 1% | 5% | 0% | 5% | 1% |
| | Urinary Frequency | 3% | 1% | 2% | 0% | — | — |
| | Urination Impaired | 3% | 0% | — | — | — | — |
| | Urinary Tract Infection | 2% | 1% | 2% | 1% | — | — |

956 1. Events reported by at least 2% of OCD, panic disorder, and social anxiety disorder in patients treated with PAXIL are
957 included, except the following events which had an incidence on placebo \geq PAXIL: [OCD]: Abdominal pain, agitation,
958 anxiety, back pain, cough increased, depression, headache, hyperkinesia, infection, paresthesia, pharyngitis, respiratory
959 disorder, rhinitis, and sinusitis. [panic disorder]: Abnormal dreams, abnormal vision, chest pain, cough increased,
960 depersonalization, depression, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, myalgia, nervousness,
961 palpitation, paresthesia, pharyngitis, rash, respiratory disorder, sinusitis, taste perversion, trauma, urination impaired, and
962 vasodilation. [social anxiety disorder]: Abdominal pain, depression, headache, infection, respiratory disorder, and
963 sinusitis.

964 2. Percentage corrected for gender.

965

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

972

973 **Table 4. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled**
974 **Clinical Trials for Generalized Anxiety Disorder and Posttraumatic Stress Disorder¹**

| 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 ² | 25% | 2% | 13% | 2% |
| | Female Genital Disorder ² | 4% | 1% | 5% | 1% |
| | Impotence ² | 4% | 3% | 9% | 1% |
| | | | | | |

975 1. Events reported by at least 2% of GAD and PTSD in patients treated with PAXIL are included, except the
976 following events which had an incidence on placebo \geq PAXIL [GAD]: Abdominal pain, back pain, trauma,
977 dyspepsia, myalgia, and pharyngitis. [PTSD]: Back pain, headache, anxiety, depression, nervousness, respiratory
978 disorder, pharyngitis, and sinusitis.

979 2. Percentage corrected for gender.

980

981 **Dose Dependency of Adverse Events:** A comparison of adverse event rates in a
982 fixed-dose study comparing 10, 20, 30, and 40 mg/day of PAXIL with placebo in the treatment
983 of major depressive disorder revealed a clear dose dependency for some of the more common
984 adverse events associated with use of PAXIL, as shown in the following table:

985

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

| 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% |

988 * Rule for including adverse events in table: Incidence at least 5% for 1 of paroxetine groups
989 and ≥ twice the placebo incidence for at least 1 paroxetine group.

990

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

995 In a fixed-dose study comparing placebo and 10, 20, and 40 mg of PAXIL in the treatment of

996 panic disorder, there was no clear relationship between adverse events and the dose of PAXIL to
 997 which patients were assigned, except for asthenia, dry mouth, anxiety, libido decreased, tremor,
 998 and abnormal ejaculation. In flexible-dose studies, no new adverse events were observed in
 999 patients receiving 60 mg of PAXIL compared to any of the other treatment groups.

1000 In a fixed-dose study comparing placebo and 20, 40, and 60 mg of PAXIL in the treatment of
 1001 social anxiety disorder, for most of the adverse events, there was no clear relationship between
 1002 adverse events and the dose of PAXIL to which patients were assigned.

1003 In a fixed-dose study comparing placebo and 20 and 40 mg of PAXIL in the treatment of
 1004 generalized anxiety disorder, for most of the adverse events, there was no clear relationship
 1005 between adverse events and the dose of PAXIL to which patients were assigned, except for the
 1006 following adverse events: Asthenia, constipation, and abnormal ejaculation.

1007 In a fixed-dose study comparing placebo and 20 and 40 mg of PAXIL in the treatment of
 1008 posttraumatic stress disorder, for most of the adverse events, there was no clear relationship
 1009 between adverse events and the dose of PAXIL to which patients were assigned, except for
 1010 impotence and abnormal ejaculation.

1011 **Adaptation to Certain Adverse Events:** Over a 4- to 6-week period, there was evidence
 1012 of adaptation to some adverse events with continued therapy (e.g., nausea and dizziness), but less
 1013 to other effects (e.g., dry mouth, somnolence, and asthenia).

1014 **Male and Female Sexual Dysfunction With SSRIs:** Although changes in sexual desire,
 1015 sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric
 1016 disorder, they may also be a consequence of pharmacologic treatment. In particular, some
 1017 evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward
 1018 sexual experiences.

1019 Reliable estimates of the incidence and severity of untoward experiences involving sexual
 1020 desire, performance, and satisfaction are difficult to obtain, however, in part because patients and
 1021 physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of
 1022 untoward sexual experience and performance cited in product labeling, are likely to
 1023 underestimate their actual incidence.

1024 In placebo-controlled clinical trials involving more than 3,200 patients, the ranges for the
 1025 reported incidence of sexual side effects in males and females with major depressive disorder,
 1026 OCD, panic disorder, social anxiety disorder, GAD, and PTSD are displayed in Table 6.
 1027

1028 **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% |

1029

1030 There are no adequate and well-controlled studies examining sexual dysfunction with
1031 paroxetine treatment.

1032 Paroxetine treatment has been associated with several cases of priapism. In those cases with a
1033 known outcome, patients recovered without sequelae.

1034 While it is difficult to know the precise risk of sexual dysfunction associated with the use of
1035 SSRIs, physicians should routinely inquire about such possible side effects.

1036 **Weight and Vital Sign Changes:** Significant weight loss may be an undesirable result of
1037 treatment with PAXIL for some patients but, on average, patients in controlled trials had minimal
1038 (about 1 pound) weight loss versus smaller changes on placebo and active control. No significant
1039 changes in vital signs (systolic and diastolic blood pressure, pulse and temperature) were
1040 observed in patients treated with PAXIL in controlled clinical trials.

1041 **ECG Changes:** In an analysis of ECGs obtained in 682 patients treated with PAXIL and
1042 415 patients treated with placebo in controlled clinical trials, no clinically significant changes
1043 were seen in the ECGs of either group.

1044 **Liver Function Tests:** In placebo-controlled clinical trials, patients treated with PAXIL
1045 exhibited abnormal values on liver function tests at no greater rate than that seen in
1046 placebo-treated patients. In particular, the PAXIL-versus-placebo comparisons for alkaline
1047 phosphatase, SGOT, SGPT, and bilirubin revealed no differences in the percentage of patients
1048 with marked abnormalities.

1049 **Hallucinations:** In pooled clinical trials of immediate-release paroxetine hydrochloride,
1050 hallucinations were observed in 22 of 9089 patients receiving drug and 4 of 3187 patients
1051 receiving placebo.

1052 **Other Events Observed During the Premarketing Evaluation of PAXIL:** During its
1053 premarketing assessment in major depressive disorder, multiple doses of PAXIL were
1054 administered to 6,145 patients in phase 2 and 3 studies. The conditions and duration of exposure
1055 to PAXIL varied greatly and included (in overlapping categories) open and double-blind studies,
1056 uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose, and titration
1057 studies. During premarketing clinical trials in OCD, panic disorder, social anxiety disorder,
1058 generalized anxiety disorder, and posttraumatic stress disorder, 542, 469, 522, 735, and 676
1059 patients, respectively, received multiple doses of PAXIL. Untoward events associated with this
1060 exposure were recorded by clinical investigators using terminology of their own choosing.
1061 Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals
1062 experiencing adverse events without first grouping similar types of untoward events into a
1063 smaller number of standardized event categories.

1064 In the tabulations that follow, reported adverse events were classified using a standard
1065 COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the
1066 proportion of the 9,089 patients exposed to multiple doses of PAXIL who experienced an event
1067 of the type cited on at least 1 occasion while receiving PAXIL. All reported events are included
1068 except those already listed in Tables 2 to 4, those reported in terms so general as to be

1069 uninformative and those events where a drug cause was remote. It is important to emphasize that
1070 although the events reported occurred during treatment with paroxetine, they were not
1071 necessarily caused by it.

1072 Events are further categorized by body system and listed in order of decreasing frequency
1073 according to the following definitions: Frequent adverse events are those occurring on 1 or more
1074 occasions in at least 1/100 patients (only those not already listed in the tabulated results from
1075 placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in
1076 1/100 to 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients. Events
1077 of major clinical importance are also described in the PRECAUTIONS section.

1078 **Body as a Whole:** *Infrequent:* Allergic reaction, chills, face edema, malaise, neck pain;
1079 *rare:* Adrenergic syndrome, cellulitis, moniliasis, neck rigidity, pelvic pain, peritonitis, sepsis,
1080 ulcer.

1081 **Cardiovascular System:** *Frequent:* Hypertension, tachycardia; *infrequent:* Bradycardia,
1082 hematoma, hypotension, migraine, postural hypotension, syncope; *rare:* Angina pectoris,
1083 arrhythmia nodal, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular
1084 accident, congestive heart failure, heart block, low cardiac output, myocardial infarct, myocardial
1085 ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis,
1086 thrombosis, varicose vein, vascular headache, ventricular extrasystoles.

1087 **Digestive System:** *Infrequent:* Bruxism, colitis, dysphagia, eructation, gastritis,
1088 gastroenteritis, gingivitis, glossitis, increased salivation, liver function tests abnormal, rectal
1089 hemorrhage, ulcerative stomatitis; *rare:* Aphthous stomatitis, bloody diarrhea, bulimia,
1090 cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal
1091 incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, intestinal obstruction,
1092 jaundice, melena, mouth ulceration, peptic ulcer, salivary gland enlargement, sialadenitis,
1093 stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries.

1094 **Endocrine System:** *Rare:* Diabetes mellitus, goiter, hyperthyroidism, hypothyroidism,
1095 thyroiditis.

1096 **Hemic and Lymphatic Systems:** *Infrequent:* Anemia, leukopenia, lymphadenopathy,
1097 purpura; *rare:* Abnormal erythrocytes, basophilia, bleeding time increased, eosinophilia,
1098 hypochromic anemia, iron deficiency anemia, leukocytosis, lymphedema, abnormal
1099 lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia,
1100 thrombocytopenia, thrombocytopenia.

1101 **Metabolic and Nutritional:** *Frequent:* Weight gain; *infrequent:* Edema, peripheral edema,
1102 SGOT increased, SGPT increased, thirst, weight loss; *rare:* Alkaline phosphatase increased,
1103 bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, gamma
1104 globulins increased, gout, hypercalcemia, hypercholesteremia, hyperglycemia, hyperkalemia,
1105 hyperphosphatemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, ketosis, lactic
1106 dehydrogenase increased, non-protein nitrogen (NPN) increased.

1107 **Musculoskeletal System:** *Frequent:* Arthralgia; *infrequent:* Arthritis, arthrosis; *rare:*
1108 Bursitis, myositis, osteoporosis, generalized spasm, tenosynovitis, tetany.

1109 **Nervous System:** *Frequent:* Emotional lability, vertigo; *infrequent:* Abnormal thinking,
1110 alcohol abuse, ataxia, dystonia, dyskinesia, euphoria, hallucinations, hostility, hypertonia,
1111 hypesthesia, hypokinesia, incoordination, lack of emotion, libido increased, manic reaction,
1112 neurosis, paralysis, paranoid reaction; *rare:* Abnormal gait, akinesia, antisocial reaction, aphasia,
1113 choreoathetosis, circumoral paresthesias, convulsion, delirium, delusions, diplopia, drug
1114 dependence, dysarthria, extrapyramidal syndrome, fasciculations, grand mal convulsion,
1115 hyperalgesia, hysteria, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy,
1116 nystagmus, peripheral neuritis, psychotic depression, psychosis, reflexes decreased, reflexes
1117 increased, stupor, torticollis, trismus, withdrawal syndrome.

1118 **Respiratory System:** *Infrequent:* Asthma, bronchitis, dyspnea, epistaxis, hyperventilation,
1119 pneumonia, respiratory flu; *rare:* Emphysema, hemoptysis, hiccups, lung fibrosis, pulmonary
1120 edema, sputum increased, stridor, voice alteration.

1121 **Skin and Appendages:** *Frequent:* Pruritus; *infrequent:* Acne, alopecia, contact dermatitis,
1122 dry skin, ecchymosis, eczema, herpes simplex, photosensitivity, urticaria; *rare:* Angioedema,
1123 erythema nodosum, erythema multiforme, exfoliative dermatitis, fungal dermatitis, furunculosis;
1124 herpes zoster, hirsutism, maculopapular rash, seborrhea, skin discoloration, skin hypertrophy,
1125 skin ulcer, sweating decreased, vesiculobullous rash.

1126 **Special Senses:** *Frequent:* Tinnitus; *infrequent:* Abnormality of accommodation,
1127 conjunctivitis, ear pain, eye pain, keratoconjunctivitis, mydriasis, otitis media; *rare:* Amblyopia,
1128 anisocoria, blepharitis, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, eye
1129 hemorrhage, glaucoma, hyperacusis, night blindness, otitis externa, parosmia, photophobia,
1130 ptosis, retinal hemorrhage, taste loss, visual field defect.

1131 **Urogenital System:** *Infrequent:* Amenorrhea, breast pain, cystitis, dysuria, hematuria,
1132 menorrhagia, nocturia, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency,
1133 vaginitis; *rare:* Abortion, breast atrophy, breast enlargement, endometrial disorder, epididymitis,
1134 female lactation, fibrocystic breast, kidney calculus, kidney pain, leukorrhea, mastitis,
1135 metrorrhagia, nephritis, oliguria, salpingitis, urethritis, urinary casts, uterine spasm, urolith,
1136 vaginal hemorrhage, vaginal moniliasis.

1137 **Postmarketing Reports:** Voluntary reports of adverse events in patients taking PAXIL that
1138 have been received since market introduction and not listed above that may have no causal
1139 relationship with the drug include acute pancreatitis, elevated liver function tests (the most
1140 severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated
1141 with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism,
1142 syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and
1143 galactorrhea, neuroleptic malignant syndrome–like events, serotonin syndrome; extrapyramidal
1144 symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia,
1145 oculogyric crisis which has been associated with concomitant use of pimozide; tremor and
1146 trismus; status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis,
1147 anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular
1148 tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, events related

1149 to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and
1150 agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura). There has been
1151 a case report of an elevated phenytoin level after 4 weeks of PAXIL and phenytoin
1152 coadministration. There has been a case report of severe hypotension when PAXIL was added to
1153 chronic metoprolol treatment.

1154 **DRUG ABUSE AND DEPENDENCE**

1155 **Controlled Substance Class:** PAXIL is not a controlled substance.

1156 **Physical and Psychologic Dependence:** PAXIL has not been systematically studied in
1157 animals or humans for its potential for abuse, tolerance or physical dependence. While the
1158 clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were
1159 not systematic and it is not possible to predict on the basis of this limited experience the extent to
1160 which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently,
1161 patients should be evaluated carefully for history of drug abuse, and such patients should be
1162 observed closely for signs of misuse or abuse of PAXIL (e.g., development of tolerance,
1163 incrementations of dose, drug-seeking behavior).

1164 **OVERDOSAGE**

1165 **Human Experience:** Since the introduction of PAXIL in the United States, 342 spontaneous
1166 cases of deliberate or accidental overdosage during paroxetine treatment have been reported
1167 worldwide (circa 1999). These include overdoses with paroxetine alone and in combination with
1168 other substances. Of these, 48 cases were fatal and of the fatalities, 17 appeared to involve
1169 paroxetine alone. Eight fatal cases that documented the amount of paroxetine ingested were
1170 generally confounded by the ingestion of other drugs or alcohol or the presence of significant
1171 comorbid conditions. Of 145 non-fatal cases with known outcome, most recovered without
1172 sequelae. The largest known ingestion involved 2,000 mg of paroxetine (33 times the maximum
1173 recommended daily dose) in a patient who recovered.

1174 Commonly reported adverse events associated with paroxetine overdosage include
1175 somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other
1176 notable signs and symptoms observed with overdoses involving paroxetine (alone or with other
1177 substances) include mydriasis, convulsions (including status epilepticus), ventricular
1178 dysrhythmias (including torsade de pointes), hypertension, aggressive reactions, syncope,
1179 hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction
1180 (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin
1181 syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

1182 **Overdosage Management:** Treatment should consist of those general measures employed in
1183 the management of overdosage with any drugs effective in the treatment of major depressive
1184 disorder.

1185 Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital
1186 signs. General supportive and symptomatic measures are also recommended. Induction of emesis
1187 is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway

1188 protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic
1189 patients.

1190 Activated charcoal should be administered. Due to the large volume of distribution of this
1191 drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of
1192 benefit. No specific antidotes for paroxetine are known.

1193 A specific caution involves patients who are taking or have recently taken paroxetine who
1194 might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the
1195 parent tricyclic and/or an active metabolite may increase the possibility of clinically significant
1196 sequelae and extend the time needed for close medical observation (see PRECAUTIONS—
1197 *Drugs Metabolized by Cytochrome CYP2D6*).

1198 In managing overdose, consider the possibility of multiple drug involvement. The physician
1199 should consider contacting a poison control center for additional information on the treatment of
1200 any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians'*
1201 *Desk Reference* (PDR).

1202 **DOSAGE AND ADMINISTRATION**

1203 **Major Depressive Disorder: Usual Initial Dosage:** PAXIL should be administered as a
1204 single daily dose with or without food, usually in the morning. The recommended initial dose is
1205 20 mg/day. Patients were dosed in a range of 20 to 50 mg/day in the clinical trials demonstrating
1206 the effectiveness of PAXIL in the treatment of major depressive disorder. As with all drugs
1207 effective in the treatment of major depressive disorder, the full effect may be delayed. Some
1208 patients not responding to a 20-mg dose may benefit from dose increases, in 10-mg/day
1209 increments, up to a maximum of 50 mg/day. Dose changes should occur at intervals of at least
1210 1 week.

1211 **Maintenance Therapy:** There is no body of evidence available to answer the question of
1212 how long the patient treated with PAXIL should remain on it. It is generally agreed that acute
1213 episodes of major depressive disorder require several months or longer of sustained
1214 pharmacologic therapy. Whether the dose needed to induce remission is identical to the dose
1215 needed to maintain and/or sustain euthymia is unknown.

1216 Systematic evaluation of the efficacy of PAXIL has shown that efficacy is maintained for
1217 periods of up to 1 year with doses that averaged about 30 mg.

1218 **Obsessive Compulsive Disorder: Usual Initial Dosage:** PAXIL should be administered
1219 as a single daily dose with or without food, usually in the morning. The recommended dose of
1220 PAXIL in the treatment of OCD is 40 mg daily. Patients should be started on 20 mg/day and the
1221 dose can be increased in 10-mg/day increments. Dose changes should occur at intervals of at
1222 least 1 week. Patients were dosed in a range of 20 to 60 mg/day in the clinical trials
1223 demonstrating the effectiveness of PAXIL in the treatment of OCD. The maximum dosage
1224 should not exceed 60 mg/day.

1225 **Maintenance Therapy:** Long-term maintenance of efficacy was demonstrated in a 6-month
1226 relapse prevention trial. In this trial, patients with OCD assigned to paroxetine demonstrated a

1227 lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY—
1228 Clinical Trials). OCD is a chronic condition, and it is reasonable to consider continuation for a
1229 responding patient. Dosage adjustments should be made to maintain the patient on the lowest
1230 effective dosage, and patients should be periodically reassessed to determine the need for
1231 continued treatment.

1232 **Panic Disorder: Usual Initial Dosage:** PAXIL should be administered as a single daily dose
1233 with or without food, usually in the morning. The target dose of PAXIL in the treatment of panic
1234 disorder is 40 mg/day. Patients should be started on 10 mg/day. Dose changes should occur in
1235 10-mg/day increments and at intervals of at least 1 week. Patients were dosed in a range of 10 to
1236 60 mg/day in the clinical trials demonstrating the effectiveness of PAXIL. The maximum dosage
1237 should not exceed 60 mg/day.

1238 **Maintenance Therapy:** Long-term maintenance of efficacy was demonstrated in a 3-month
1239 relapse prevention trial. In this trial, patients with panic disorder assigned to paroxetine
1240 demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL
1241 PHARMACOLOGY—Clinical Trials). Panic disorder is a chronic condition, and it is reasonable
1242 to consider continuation for a responding patient. Dosage adjustments should be made to
1243 maintain the patient on the lowest effective dosage, and patients should be periodically
1244 reassessed to determine the need for continued treatment.

1245 **Social Anxiety Disorder: Usual Initial Dosage:** PAXIL should be administered as a single
1246 daily dose with or without food, usually in the morning. The recommended and initial dosage is
1247 20 mg/day. In clinical trials the effectiveness of PAXIL was demonstrated in patients dosed in a
1248 range of 20 to 60 mg/day. While the safety of PAXIL has been evaluated in patients with social
1249 anxiety disorder at doses up to 60 mg/day, available information does not suggest any additional
1250 benefit for doses above 20 mg/day (see CLINICAL PHARMACOLOGY—Clinical Trials).

1251 **Maintenance Therapy:** There is no body of evidence available to answer the question of
1252 how long the patient treated with PAXIL should remain on it. Although the efficacy of PAXIL
1253 beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials, social anxiety
1254 disorder is recognized as a chronic condition, and it is reasonable to consider continuation of
1255 treatment for a responding patient. Dosage adjustments should be made to maintain the patient
1256 on the lowest effective dosage, and patients should be periodically reassessed to determine the
1257 need for continued treatment.

1258 **Generalized Anxiety Disorder: Usual Initial Dosage:** PAXIL should be administered as a
1259 single daily dose with or without food, usually in the morning. In clinical trials the effectiveness
1260 of PAXIL was demonstrated in patients dosed in a range of 20 to 50 mg/day. The recommended
1261 starting dosage and the established effective dosage is 20 mg/day. There is not sufficient
1262 evidence to suggest a greater benefit to doses higher than 20 mg/day. Dose changes should occur
1263 in 10 mg/day increments and at intervals of at least 1 week.

1264 **Maintenance Therapy:** Systematic evaluation of continuing PAXIL for periods of up to
1265 24 weeks in patients with Generalized Anxiety Disorder who had responded while taking PAXIL
1266 during an 8-week acute treatment phase has demonstrated a benefit of such maintenance (see

1267 CLINICAL PHARMACOLOGY—Clinical Trials). Nevertheless, patients should be periodically
1268 reassessed to determine the need for maintenance treatment.

1269 **Posttraumatic Stress Disorder: Usual Initial Dosage:** PAXIL should be administered as
1270 a single daily dose with or without food, usually in the morning. The recommended starting
1271 dosage and the established effective dosage is 20 mg/day. In 1 clinical trial, the effectiveness of
1272 PAXIL was demonstrated in patients dosed in a range of 20 to 50 mg/day. However, in a fixed
1273 dose study, there was not sufficient evidence to suggest a greater benefit for a dose of 40 mg/day
1274 compared to 20 mg/day. Dose changes, if indicated, should occur in 10 mg/day increments and at
1275 intervals of at least 1 week.

1276 **Maintenance Therapy:** There is no body of evidence available to answer the question of
1277 how long the patient treated with PAXIL should remain on it. Although the efficacy of PAXIL
1278 beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials, PTSD is
1279 recognized as a chronic condition, and it is reasonable to consider continuation of treatment for a
1280 responding patient. Dosage adjustments should be made to maintain the patient on the lowest
1281 effective dosage, and patients should be periodically reassessed to determine the need for
1282 continued treatment.

1283 **Special Populations: Treatment of Pregnant Women During the Third Trimester:**
1284 Neonates exposed to PAXIL and other SSRIs or SNRIs, late in the third trimester have
1285 developed complications requiring prolonged hospitalization, respiratory support, and tube
1286 feeding (see WARNINGS). When treating pregnant women with paroxetine during the third
1287 trimester, the physician should carefully consider the potential risks and benefits of treatment.
1288 The physician may consider tapering paroxetine in the third trimester.

1289 **Dosage for Elderly or Debilitated Patients, and Patients With Severe Renal or
1290 Hepatic Impairment:** The recommended initial dose is 10 mg/day for elderly patients,
1291 debilitated patients, and/or patients with severe renal or hepatic impairment. Increases may be
1292 made if indicated. Dosage should not exceed 40 mg/day.

1293 **Switching Patients to or From a Monoamine Oxidase Inhibitor:** At least 14 days
1294 should elapse between discontinuation of an MAOI and initiation of therapy with PAXIL.
1295 Similarly, at least 14 days should be allowed after stopping PAXIL before starting an MAOI.

1296 **Discontinuation of Treatment With PAXIL:** Symptoms associated with discontinuation of
1297 PAXIL have been reported (see PRECAUTIONS). Patients should be monitored for these
1298 symptoms when discontinuing treatment, regardless of the indication for which PAXIL is being
1299 prescribed. A gradual reduction in the dose rather than abrupt cessation is recommended
1300 whenever possible. If intolerable symptoms occur following a decrease in the dose or upon
1301 discontinuation of treatment, then resuming the previously prescribed dose may be considered.
1302 Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

1303 **NOTE:** SHAKE SUSPENSION WELL BEFORE USING.

1304 HOW SUPPLIED

1305 **Tablets:** Film-coated, modified-oval as follows:

- 1306 10-mg yellow, scored tablets engraved on the front with PAXIL and on the back with 10.
1307 NDC 0029-3210-13 Bottles of 30
1308 20-mg pink, scored tablets engraved on the front with PAXIL and on the back with 20.
1309 NDC 0029-3211-13 Bottles of 30
1310 NDC 0029-3211-59 Bottles of 90
1311 NDC 0029-3211-21 SUP 100s (intended for institutional use only)
1312 30-mg blue tablets engraved on the front with PAXIL and on the back with 30.
1313 NDC 0029-3212-13 Bottles of 30
1314 40-mg green tablets engraved on the front with PAXIL and on the back with 40.
1315 NDC 0029-3213-13 Bottles of 30
1316 Store tablets between 15° and 30°C (59° and 86°F).
1317 **Oral Suspension:** Orange-colored, orange-flavored, 10 mg/5 mL, in 250 mL white bottles.
1318 NDC 0029-3215-48
1319 Store suspension at or below 25°C (77°F).
1320 PAXIL is a registered trademark of GlaxoSmithKline.
1321

Medication Guide

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

PAXIL[®] (PAX-il) (paroxetine hydrochloride) Tablets and Oral Suspension

1322
1323
1324
1325
1326
1327
1328 Read the Medication Guide that comes with your or your family member's antidepressant
1329 medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with
1330 antidepressant medicines. **Talk to your, or your family member's, healthcare provider**
1331 **about:**

- 1332 • All risks and benefits of treatment with antidepressant medicines
- 1333 • All treatment choices for depression or other serious mental illness

1334
1335 **What is the most important information I should know about antidepressant medicines,**
1336 **depression and other serious mental illnesses, and suicidal thoughts or action?**

- 1337
1338 **1. Antidepressant medicines may increase suicidal thoughts and actions in some children,**
1339 **teenagers, and young adults within the first few months of treatment.**
1340
- 1341 **2. Depression and other serious mental illnesses are the most important causes of suicidal**
1342 **thoughts and actions. Some people may have a particularly high risk of having suicidal**
1343 **thoughts or actions.** These include people who have (or have a family history of) bipolar
1344 illness (also called manic-depressive illness) or suicidal thoughts or actions.
1345
- 1346 **3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a**

1347 **family member?**

- 1348 • Pay close attention to any changes, especially sudden changes, in mood, behaviors,
1349 thoughts, or feelings. This is very important when an antidepressant is started or when the
1350 dose is changed.
- 1351 • Call the healthcare provider right away to report new or sudden changes in mood,
1352 behavior, thoughts, or feelings.
- 1353 • Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare
1354 provider between visits as needed, especially if you have concerns about symptoms.

1355

1356 **Call a healthcare provider right away if you or your family member has any of the**
1357 **following symptoms, especially if they are new, worse, or worry you:**

- 1358 • Thoughts about suicide or dying
- 1359 • Attempts to commit suicide
- 1360 • New or worse depression
- 1361 • New or worse anxiety
- 1362 • Feeling very agitated or restless
- 1363 • Panic attacks
- 1364 • Trouble sleeping (insomnia)
- 1365 • New or worse irritability
- 1366 • Acting aggressive, being angry, or violent
- 1367 • Acting on dangerous impulses
- 1368 • An extreme increase in activity and talking (mania)
- 1369 • Other unusual changes in behavior or mood

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1371 **What else do I need to know about antidepressant medicines?**

1372

- 1373 • **Never stop an antidepressant medicine without first talking to a healthcare**
1374 **provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- 1375
- 1376 • **Antidepressants are medicines used to treat depression and other illnesses.** It is
1377 important to discuss all the risk of treating depression and also the risks of not treating it.
1378 Patients and their families or other caregivers should discuss all treatment choices with
1379 the healthcare provider, not just the use of antidepressants.
- 1380
- 1381 • **Antidepressant medicines have other side effects.** Talk to the healthcare provider about
1382 the side effects of the medicine prescribed for you or your family member.
- 1383
- 1384 • **Antidepressant medicines can interact with other medicines.** Know all of the
1385 medicines that you or your family member takes. Keep a list of all medicines to show the
1386 healthcare provider. Do not start new medicines without first checking with your
1387 healthcare provider.
- 1388
- 1389 • **Not all antidepressant medicines prescribed for children are FDA approved for use**

1390 **in children.** Talk to your child's healthcare provider for more information.

1391

1392 This Medication Guide has been approved by the U.S. Food and Drug Administration for all
1393 antidepressants.

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