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2
3 **PAXIL[®]**
4 **(paroxetine hydrochloride)**
5 **Tablets and Oral Suspension**
6

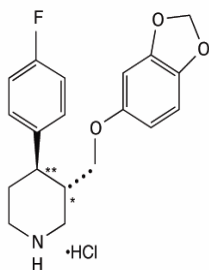
7 **Suicidality in Children and Adolescents**

8 Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in
9 short-term studies in children and adolescents with Major Depressive Disorder (MDD) and
10 other psychiatric disorders. Anyone considering the use of PAXIL or any other
11 antidepressant in a child or adolescent must balance this risk with the clinical need.
12 Patients who are started on therapy should be observed closely for clinical worsening,
13 suicidality, or unusual changes in behavior. Families and caregivers should be advised of
14 the need for close observation and communication with the prescriber. PAXIL is not
15 approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS—Pediatric
16 Use.)

17 Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of
18 9 antidepressant drugs (SSRIs and others) in children and adolescents with major
19 depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric
20 disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of
21 adverse events representing suicidal thinking or behavior (suicidality) during the first few
22 months of treatment in those receiving antidepressants. The average risk of such events in
23 patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides
24 occurred in these trials.

25 **DESCRIPTION**

26 PAXIL (paroxetine hydrochloride) is an orally administered psychotropic drug. It is the
27 hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-*trans*-4*R*-(4'-
28 fluorophenyl)-3*S*-[(3',4'-methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate
29 and has the empirical formula of C₁₉H₂₀FNO₃•HCl•1/2H₂O. The molecular weight is 374.8
30 (329.4 as free base). The structural formula of paroxetine hydrochloride is:



31
32 Paroxetine hydrochloride is an odorless, off-white powder, having a melting point range of
33 120° to 138°C and a solubility of 5.4 mg/mL in water.

34 **Tablets:** Each film-coated tablet contains paroxetine hydrochloride equivalent to paroxetine as
35 follows: 10 mg–yellow (scored); 20 mg–pink (scored); 30 mg–blue, 40 mg–green. Inactive
36 ingredients consist of dibasic calcium phosphate dihydrate, hypromellose, magnesium stearate,
37 polyethylene glycols, polysorbate 80, sodium starch glycolate, titanium dioxide, and 1 or more of
38 the following: D&C Red No. 30, D&C Yellow No. 10, FD&C Blue No. 2, FD&C Yellow No. 6.
39 **Suspension for Oral Administration:** Each 5 mL of orange-colored, orange-flavored liquid
40 contains paroxetine hydrochloride equivalent to paroxetine, 10 mg. Inactive ingredients consist
41 of polacrillin potassium, microcrystalline cellulose, propylene glycol, glycerin, sorbitol, methyl
42 paraben, propyl paraben, sodium citrate dihydrate, citric acid anhydrate, sodium saccharin,
43 flavorings, FD&C Yellow No. 6, and simethicone emulsion, USP.

44 **CLINICAL PHARMACOLOGY**

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

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

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

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

70 Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the
71 hydrochloride salt. In a study in which normal male subjects (n = 15) received 30 mg tablets
72 daily for 30 days, steady-state paroxetine concentrations were achieved by approximately

73 10 days for most subjects, although it may take substantially longer in an occasional patient. At
74 steady state, mean values of C_{\max} , T_{\max} , C_{\min} , and $T_{1/2}$ were 61.7 ng/mL (CV 45%), 5.2 hr.
75 (CV 10%), 30.7 ng/mL (CV 67%), and 21.0 hours (CV 32%), respectively. The steady-state C_{\max}
76 and C_{\min} values were about 6 and 14 times what would be predicted from single-dose studies.
77 Steady-state drug exposure based on AUC_{0-24} was about 8 times greater than would have been
78 predicted from single-dose data in these subjects. The excess accumulation is a consequence of
79 the fact that 1 of the enzymes that metabolizes paroxetine is readily saturable.

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

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

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

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

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

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

110 **Other Clinical Pharmacology Information: Specific Populations: Renal and Liver**
111 **Disease:** Increased plasma concentrations of paroxetine occur in subjects with renal and hepatic
112 impairment. The mean plasma concentrations in patients with creatinine clearance below

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

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

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

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

127 **Clinical Trials**

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

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

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

152 daily). In this study, patients receiving paroxetine experienced a mean reduction of
153 approximately 7 points on the YBOCS total score, which was significantly greater than the mean
154 reduction of approximately 4 points in placebo-treated patients.

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

157

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

158

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

223 Study 2 was a flexible-dose study comparing paroxetine (20 mg to 50 mg daily) and placebo.
224 PAXIL demonstrated statistically significant superiority over placebo on the Hamilton Rating
225 Scale for Anxiety (HAM-A) total score. A third study, also flexible-dose comparing paroxetine
226 (20 mg to 50 mg daily), did not demonstrate statistically significant superiority of PAXIL over
227 placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score, the primary outcome.

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

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

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

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

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

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

264 The majority of patients in these trials were women (68% women: 377 out of 551 subjects in
265 Study 1 and 66% women: 202 out of 303 subjects in Study 2). Subgroup analyses did not
266 indicate differences in treatment outcomes as a function of gender. There were an insufficient
267 number of patients who were 65 years and older or were non-Caucasian to conduct subgroup
268 analyses on the basis of age or race, respectively.

269 **INDICATIONS AND USAGE**

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

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

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

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

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

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

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

297 Long-term maintenance of efficacy was demonstrated in a 6-month relapse prevention trial. In
298 this trial, patients assigned to paroxetine showed a lower relapse rate compared to patients on
299 placebo (see CLINICAL PHARMACOLOGY—Clinical Trials). Nevertheless, the physician

300 who elects to use PAXIL for extended periods should periodically re-evaluate the long-term
301 usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).
302 **Panic Disorder:** PAXIL is indicated for the treatment of panic disorder, with or without
303 agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of
304 unexpected panic attacks and associated concern about having additional attacks, worry about
305 the implications or consequences of the attacks, and/or a significant change in behavior related to
306 the attacks.

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

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

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

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

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

336 The effectiveness of PAXIL in long-term treatment of social anxiety disorder, i.e., for more
337 than 12 weeks, has not been systematically evaluated in adequate and well-controlled trials.
338 Therefore, the physician who elects to prescribe PAXIL for extended periods should periodically

339 re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND
340 ADMINISTRATION).

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

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

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

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

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

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

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

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

382 **CONTRAINDICATIONS**

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

385 Concomitant use in patients taking pimozone is contraindicated (see PRECAUTIONS).

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

388 **WARNINGS**

389 **Clinical Worsening and Suicide Risk:** Patients with major depressive disorder (MDD),
390 both adult and pediatric, may experience worsening of their depression and/or the emergence of
391 suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they
392 are taking antidepressant medications, and this risk may persist until significant remission
393 occurs. There has been a long-standing concern that antidepressants may have a role in inducing
394 worsening of depression and the emergence of suicidality in certain patients. Antidepressants
395 increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children
396 and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

397 Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and
398 others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of
399 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events
400 representing suicidal behavior or thinking (suicidality) during the first few months of treatment
401 in those receiving antidepressants. The average risk of such events in patients receiving
402 antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk
403 among drugs, but a tendency toward an increase for almost all drugs studied. The risk of
404 suicidality was most consistently observed in the MDD trials, but there were signals of risk
405 arising from some trials in other psychiatric indications (obsessive compulsive disorder and
406 social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown
407 whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several
408 months.

409 **All pediatric patients being treated with antidepressants for any indication should be**
410 **observed closely for clinical worsening, suicidality, and unusual changes in behavior,**
411 **especially during the initial few months of a course of drug therapy, or at times of dose**
412 **changes, either increases or decreases. Such observation would generally include at least**
413 **weekly face-to-face contact with patients or their family members or caregivers during the**
414 **first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at**
415 **12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may**
416 **be appropriate between face-to-face visits.**

417 **Adults with MDD or co-morbid depression in the setting of other psychiatric illness**
418 **being treated with antidepressants should be observed similarly for clinical worsening and**
419 **suicidality, especially during the initial few months of a course of drug therapy, or at times**
420 **of dose changes, either increases or decreases.**

421 Young adults, especially those with MDD, may be at increased risk for suicidal behavior
422 during treatment with paroxetine. An analysis of placebo-controlled trials of adults with
423 psychiatric disorders showed a higher frequency of suicidal behavior in young adults
424 (prospectively defined as aged 18-24 years) treated with paroxetine compared with placebo
425 (17/776 [2.19%] versus 5/542 [0.92%]), although this difference was not statistically significant.
426 In the older age groups (aged 25-64 years and ≥ 65 years), no such increase was observed. In
427 adults with MDD (all ages), there was a statistically significant increase in the frequency of
428 suicidal behavior in patients treated with paroxetine compared with placebo (11/3,455 [0.32%]
429 versus 1/1,978 [0.05%]); all of the events were suicide attempts. However, the majority of these
430 attempts for paroxetine (8 of 11) were in younger adults aged 18-30 years. These MDD data
431 suggest that the higher frequency observed in the younger adult population across psychiatric
432 disorders may extend beyond the age of 24.

433 **In addition, patients with a history of suicidal behavior or thoughts, those patients**
434 **exhibiting a significant degree of suicidal ideation prior to commencement of treatment,**
435 **and young adults, are at an increased risk of suicidal thoughts or suicide attempts, and**
436 **should receive careful monitoring during treatment.**

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

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

449 If the decision has been made to discontinue treatment, medication should be tapered, as
450 rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with
451 certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION—
452 Discontinuation of Treatment With PAXIL, for a description of the risks of discontinuation of
453 PAXIL).

454 **Families and caregivers of pediatric patients being treated with antidepressants for**
455 **major depressive disorder or other indications, both psychiatric and nonpsychiatric,**
456 **should be alerted about the need to monitor patients for the emergence of agitation,**

457 irritability, unusual changes in behavior, and the other symptoms described above, as well
458 as the emergence of suicidality, and to report such symptoms immediately to health care
459 providers. Such monitoring should include daily observation by families and caregivers.
460 Prescriptions for PAXIL should be written for the smallest quantity of tablets consistent with
461 good patient management, in order to reduce the risk of overdose. Families and caregivers of
462 adults being treated for depression should be similarly advised.

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

472 **Potential for Interaction With Monoamine Oxidase Inhibitors:** In patients receiving
473 another serotonin reuptake inhibitor drug in combination with a monoamine oxidase
474 inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including
475 hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of
476 vital signs, and mental status changes that include extreme agitation progressing to
477 delirium and coma. These reactions have also been reported in patients who have recently
478 discontinued that drug and have been started on an MAOI. Some cases presented with
479 features resembling neuroleptic malignant syndrome. While there are no human data
480 showing such an interaction with PAXIL, limited animal data on the effects of combined
481 use of paroxetine and MAOIs suggest that these drugs may act synergistically to elevate
482 blood pressure and evoke behavioral excitation. Therefore, it is recommended that PAXIL
483 not be used in combination with an MAOI, or within 14 days of discontinuing treatment
484 with an MAOI. At least 2 weeks should be allowed after stopping PAXIL before starting an
485 MAOI.

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

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

494 **Usage in Pregnancy: Teratogenic Effects:** Epidemiological studies have shown that
495 infants born to women who had first trimester paroxetine exposure had an increased risk of
496 cardiovascular malformations, primarily ventricular and atrial septal defects (VSDs and ASDs).

497 In general, septal defects range from those that are symptomatic and may require surgery to those
498 that are asymptomatic and may resolve spontaneously. If a patient becomes pregnant while
499 taking paroxetine, she should be advised of the potential harm to the fetus. Unless the benefits of
500 paroxetine to the mother justify continuing treatment, consideration should be given to either
501 discontinuing paroxetine therapy or switching to another antidepressant (see PRECAUTIONS—
502 Discontinuation of Treatment with PAXIL). For women who intend to become pregnant or are in
503 their first trimester of pregnancy, paroxetine should only be initiated after consideration of the
504 other available treatment options.

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

513 A separate retrospective cohort study using US United Healthcare data evaluated 5,956 infants
514 of mothers dispensed paroxetine or other antidepressants during the first trimester (n = 815 for
515 paroxetine). This study showed a trend towards an increased risk for cardiovascular
516 malformations for paroxetine compared to other antidepressants (OR 1.5; 95% confidence
517 interval 0.8-2.9). The prevalence of cardiovascular malformations following first trimester
518 dispensing was 1.5% for paroxetine vs. 1% for other antidepressants. Nine out of 12 infants with
519 cardiovascular malformations whose mothers were dispensed paroxetine in the first trimester had
520 VSDs. This study also suggested an increased risk of overall major congenital malformations
521 (inclusive of the cardiovascular defects) for paroxetine compared to other antidepressants (OR
522 1.8; 95% confidence interval 1.2-2.8). The prevalence of all congenital malformations following
523 first trimester exposure was 4% for paroxetine vs. 2% for other antidepressants.

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

532 **Nonteratogenic Effects:** Neonates exposed to PAXIL and other SSRIs or serotonin and
533 norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed
534 complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such
535 complications can arise immediately upon delivery. Reported clinical findings have included
536 respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty,

537 vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and
538 constant crying. These features are consistent with either a direct toxic effect of SSRIs and
539 SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the
540 clinical picture is consistent with serotonin syndrome (see WARNINGS—Potential for
541 Interaction With Monoamine Oxidase Inhibitors).

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

544 When treating a pregnant woman with paroxetine during the third trimester, the physician
545 should carefully consider the potential risks and benefits of treatment (see DOSAGE AND
546 ADMINISTRATION).

547 **PRECAUTIONS**

548 **General: Activation of Mania/Hypomania:** During premarketing testing, hypomania or
549 mania occurred in approximately 1.0% of unipolar patients treated with PAXIL compared to
550 1.1% of active-control and 0.3% of placebo-treated unipolar patients. In a subset of patients
551 classified as bipolar, the rate of manic episodes was 2.2% for PAXIL and 11.6% for the
552 combined active-control groups. As with all drugs effective in the treatment of major depressive
553 disorder, PAXIL should be used cautiously in patients with a history of mania.

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

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

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

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

574 Patients should be monitored for these symptoms when discontinuing treatment with PAXIL.
575 A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible.

576 If intolerable symptoms occur following a decrease in the dose or upon discontinuation of
577 treatment, then resuming the previously prescribed dose may be considered. Subsequently, the
578 physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND
579 ADMINISTRATION).

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

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

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

590 **Serotonin Syndrome:** The development of a serotonin syndrome may occur in association
591 with treatment with paroxetine, particularly with concomitant use of serotonergic drugs and with
592 drugs which may have impaired metabolism of paroxetine. Symptoms have included agitation,
593 confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia, and
594 tremor. The concomitant use of PAXIL with serotonin precursors (such as tryptophan) is not
595 recommended (see WARNINGS—Potential for Interaction with Monoamine Oxidase Inhibitors
596 and PRECAUTIONS—Drug Interactions).

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

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

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

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

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

625 **Information for Patients:** Prescribers or other health professionals should inform patients,
626 their families, and their caregivers about the benefits and risks associated with treatment with
627 PAXIL and should counsel them in its appropriate use. A patient Medication Guide About Using
628 Antidepressants in Children and Teenagers is available for PAXIL. The prescriber or health
629 professional should instruct patients, their families, and their caregivers to read the Medication
630 Guide and should assist them in understanding its contents. Patients should be given the
631 opportunity to discuss the contents of the Medication Guide and to obtain answers to any
632 questions they may have. The complete text of the Medication Guide is reprinted at the end of
633 this document.

634 **Information from clinical trials has suggested that young adults, particularly those with
635 depression, may be at an increased risk of suicidal behavior (including suicide attempts) when
636 treated with PAXIL. The majority of attempted suicides in clinical trials in depression involved
637 patients aged 18-30 years.**

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

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

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

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

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

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

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

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

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

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

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

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

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

684 **Serotonergic Drugs:** Based on the mechanism of action of paroxetine and the potential for
685 serotonin syndrome, caution is advised when PAXIL is coadministered with other drugs or
686 agents that may affect the serotonergic neurotransmitter systems, such as tryptophan, triptans,
687 serotonin reuptake inhibitors, linezolid (an antibiotic which is a reversible non-selective MAOI),
688 lithium, tramadol, or St. John's Wort (see Serotonin Syndrome).

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

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

695 **Triptans:** There have been rare postmarketing reports describing patients with weakness,
696 hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor
697 (SSRI) and sumatriptan. If concomitant treatment with a triptan and an SSRI (e.g., fluoxetine,
698 fluvoxamine, paroxetine, sertraline) is clinically warranted, appropriate observation of the patient
699 is advised (see Serotonin Syndrome).

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

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

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

718 **Phenytoin:** When a single oral 30-mg dose of PAXIL was administered at phenytoin steady
719 state (300 mg once daily for 14 days), paroxetine AUC and T_{1/2} were reduced (by an average of
720 50% and 35%, respectively) compared to PAXIL administered alone. In a separate study, when a
721 single oral 300-mg dose of phenytoin was administered at paroxetine steady state (30 mg once
722 daily for 14 days), phenytoin AUC was slightly reduced (12% on average) compared to
723 phenytoin administered alone. Since both drugs exhibit nonlinear pharmacokinetics, the above
724 studies may not address the case where the 2 drugs are both being chronically dosed. No initial
725 dosage adjustments are considered necessary when these drugs are coadministered; any
726 subsequent adjustments should be guided by clinical effect (see ADVERSE REACTIONS—
727 Postmarketing Reports).

728 **Drugs Metabolized by CYP2D6:** Many drugs, including most drugs effective in the
729 treatment of major depressive disorder (paroxetine, other SSRIs and many tricyclics), are
730 metabolized by the cytochrome P₄₅₀ isozyme CYP2D6. Like other agents that are metabolized by
731 CYP2D6, paroxetine may significantly inhibit the activity of this isozyme. In most patients
732 (>90%), this CYP2D6 isozyme is saturated early during dosing with PAXIL. In 1 study, daily
733 dosing of PAXIL (20 mg once daily) under steady-state conditions increased single dose
734 desipramine (100 mg) C_{max}, AUC, and T_{1/2} by an average of approximately 2-, 5-, and 3-fold,

735 respectively. Concomitant use of paroxetine with risperidone, a CYP2D6 substrate has also been
736 evaluated. In 1 study, daily dosing of paroxetine 20 mg in patients stabilized on risperidone (4 to
737 8 mg/day) increased mean plasma concentrations of risperidone approximately 4-fold, decreased
738 9-hydroxyrisperidone concentrations approximately 10%, and increased concentrations of the
739 active moiety (the sum of risperidone plus 9-hydroxyrisperidone) approximately 1.4-fold. The
740 effect of paroxetine on the pharmacokinetics of atomoxetine has been evaluated when both drugs
741 were at steady state. In healthy volunteers who were extensive metabolizers of CYP2D6,
742 paroxetine 20 mg daily was given in combination with 20 mg atomoxetine every 12 hours. This
743 resulted in increases in steady state atomoxetine AUC values that were 6- to 8-fold greater and in
744 atomoxetine C_{max} values that were 3- to 4-fold greater than when atomoxetine was given alone.
745 Dosage adjustment of atomoxetine may be necessary and it is recommended that atomoxetine be
746 initiated at a reduced dose when it is given with paroxetine.

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

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

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

758 At steady state, when the CYP2D6 pathway is essentially saturated, paroxetine clearance is
759 governed by alternative P_{450} isozymes that, unlike CYP2D6, show no evidence of saturation (see
760 PRECAUTIONS—*Tricyclic Antidepressants*).

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

771 **Tricyclic Antidepressants (TCAs):** Caution is indicated in the coadministration of
772 tricyclic antidepressants (TCAs) with PAXIL, because paroxetine may inhibit TCA metabolism.
773 Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be

774 reduced, if a TCA is coadministered with PAXIL (see PRECAUTIONS—*Drugs Metabolized by*
775 *Cytochrome CYP2D6*).

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

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

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

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

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

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

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

803 **Beta-Blockers:** In a study where propranolol (80 mg twice daily) was dosed orally for
804 18 days, the established steady-state plasma concentrations of propranolol were unaltered during
805 coadministration with PAXIL (30 mg once daily) for the final 10 days. The effects of
806 propranolol on paroxetine have not been evaluated (see ADVERSE REACTIONS—
807 Postmarketing Reports).

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

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

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

817 **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** Two-year
818 carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and
819 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to 2.4 (mouse) and
820 3.9 (rat) times the maximum recommended human dose (MRHD) for major depressive disorder,
821 social anxiety disorder, GAD, and PTSD on a mg/m² basis. Because the MRHD for major
822 depressive disorder is slightly less than that for OCD (50 mg versus 60 mg), the doses used in
823 these carcinogenicity studies were only 2.0 (mouse) and 3.2 (rat) times the MRHD for OCD.
824 There was a significantly greater number of male rats in the high-dose group with reticulum cell
825 sarcomas (1/100, 0/50, 0/50, and 4/50 for control, low-, middle-, and high-dose groups,
826 respectively) and a significantly increased linear trend across dose groups for the occurrence of
827 lymphoreticular tumors in male rats. Female rats were not affected. Although there was a
828 dose-related increase in the number of tumors in mice, there was no drug-related increase in the
829 number of mice with tumors. The relevance of these findings to humans is unknown.

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

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

843 **Pregnancy:** Pregnancy Category D. See WARNINGS—Usage in Pregnancy: *Teratogenic and*
844 *Nonteratogenic Effects.*

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

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

848 **Pediatric Use:** Safety and effectiveness in the pediatric population have not been established
849 (see BOX WARNING and WARNINGS—Clinical Worsening and Suicide Risk). Three
850 placebo-controlled trials in 752 pediatric patients with MDD have been conducted with PAXIL,
851 and the data were not sufficient to support a claim for use in pediatric patients. Anyone

852 considering the use of PAXIL in a child or adolescent must balance the potential risks with the
853 clinical need.

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

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

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

870 **ADVERSE REACTIONS**

871 **Associated With Discontinuation of Treatment:** Twenty percent (1,199/6,145) of patients
872 treated with PAXIL in worldwide clinical trials in major depressive disorder and 16.1%
873 (84/522), 11.8% (64/542), 9.4% (44/469), 10.7% (79/735), and 11.7% (79/676) of patients
874 treated with PAXIL in worldwide trials in social anxiety disorder, OCD, panic disorder, GAD,
875 and PTSD, respectively, discontinued treatment due to an adverse event. The most common
876 events ($\geq 1\%$) associated with discontinuation and considered to be drug related (i.e., those events
877 associated with dropout at a rate approximately twice or greater for PAXIL compared to placebo)
878 included the following:

879

	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%			—	—

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

882 1. Incidence corrected for gender.

883

884 **Commonly Observed Adverse Events: Major Depressive Disorder:** The most
885 commonly observed adverse events associated with the use of paroxetine (incidence of 5% or
886 greater and incidence for PAXIL at least twice that for placebo, derived from Table 1) were:
887 Asthenia, sweating, nausea, decreased appetite, somnolence, dizziness, insomnia, tremor,
888 nervousness, ejaculatory disturbance, and other male genital disorders.

889 **Obsessive Compulsive Disorder:** The most commonly observed adverse events
890 associated with the use of paroxetine (incidence of 5% or greater and incidence for PAXIL at
891 least twice that of placebo, derived from Table 2) were: Nausea, dry mouth, decreased appetite,
892 constipation, dizziness, somnolence, tremor, sweating, impotence, and abnormal ejaculation.

893 **Panic Disorder:** The most commonly observed adverse events associated with the use of
894 paroxetine (incidence of 5% or greater and incidence for PAXIL at least twice that for placebo,
895 derived from Table 2) were: Asthenia, sweating, decreased appetite, libido decreased, tremor,
896 abnormal ejaculation, female genital disorders, and impotence.

897 **Social Anxiety Disorder:** The most commonly observed adverse events associated with
898 the use of paroxetine (incidence of 5% or greater and incidence for PAXIL at least twice that for
899 placebo, derived from Table 2) were: Sweating, nausea, dry mouth, constipation, decreased
900 appetite, somnolence, tremor, libido decreased, yawn, abnormal ejaculation, female genital
901 disorders, and impotence.

902 **Generalized Anxiety Disorder:** The most commonly observed adverse events associated
903 with the use of paroxetine (incidence of 5% or greater and incidence for PAXIL at least twice
904 that for placebo, derived from Table 3) were: Asthenia, infection, constipation, decreased
905 appetite, dry mouth, nausea, libido decreased, somnolence, tremor, sweating, and abnormal
906 ejaculation.

907 **Posttraumatic Stress Disorder:** The most commonly observed adverse events associated
908 with the use of paroxetine (incidence of 5% or greater and incidence for PAXIL at least twice
909 that for placebo, derived from Table 3) were: Asthenia, sweating, nausea, dry mouth, diarrhea,
910 decreased appetite, somnolence, libido decreased, abnormal ejaculation, female genital disorders,
911 and impotence.

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

920 **Major Depressive Disorder:** Table 1 enumerates adverse events that occurred at an
921 incidence of 1% or more among paroxetine-treated patients who participated in short-term
922 (6-week) placebo-controlled trials in which patients were dosed in a range of 20 mg to
923 50 mg/day. Reported adverse events were classified using a standard COSTART-based
924 Dictionary terminology.

925

926 **Table 1. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled**
 927 **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%

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

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

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

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

950 **Table 2. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled**
 951 **Clinical Trials for Obsessive Compulsive Disorder, Panic Disorder, and Social Anxiety**
 952 **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%	—	—	

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

961 2. Percentage corrected for gender.

962

963 **Generalized Anxiety Disorder and Posttraumatic Stress Disorder:** Table 3
 964 enumerates adverse events that occurred at a frequency of 2% or more among GAD patients on
 965 PAXIL who participated in placebo-controlled trials of 8-weeks duration in which patients were
 966 dosed in a range of 10 mg/day to 50 mg/day or among PTSD patients on PAXIL who
 967 participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a
 968 range of 20 mg/day to 50 mg/day.

969

970 **Table 3. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled**
 971 **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%
Respiratory System	Abnormal Dreams			3%	2%
	Respiratory Disorder	7%	5%	—	—
	Sinusitis	4%	3%	—	—
Special Senses	Yawn	4%	—	2%	<1%
	Abnormal Vision	2%	1%	3%	1%
Urogenital System	Abnormal	25%	2%	13%	2%
	Ejaculation ²				
	Female Genital Disorder ²	4%	1%	5%	1%
	Impotence ²	4%	3%	9%	1%

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

976 2. Percentage corrected for gender.

977

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

982

983 **Table 4 . Treatment-Emergent Adverse Experience Incidence in a Dose-Comparison Trial**
984 **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%

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

987

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

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

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

1000 In a fixed-dose study comparing placebo and 20 and 40 mg of PAXIL in the treatment of
1001 generalized anxiety disorder, for most of the adverse events, there was no clear relationship
1002 between adverse events and the dose of PAXIL to which patients were assigned, except for the
1003 following adverse events: Asthenia, constipation, and abnormal ejaculation.

1004 In a fixed-dose study comparing placebo and 20 and 40 mg of PAXIL in the treatment of
1005 posttraumatic stress disorder, for most of the adverse events, there was no clear relationship
1006 between adverse events and the dose of PAXIL to which patients were assigned, except for
1007 impotence and abnormal ejaculation.

1008 **Adaptation to Certain Adverse Events:** Over a 4- to 6-week period, there was evidence
1009 of adaptation to some adverse events with continued therapy (e.g., nausea and dizziness), but less
1010 to other effects (e.g., dry mouth, somnolence, and asthenia).

1011 **Male and Female Sexual Dysfunction With SSRIs:** Although changes in sexual desire,
1012 sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric
1013 disorder, they may also be a consequence of pharmacologic treatment. In particular, some
1014 evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward
1015 sexual experiences.

1016 Reliable estimates of the incidence and severity of untoward experiences involving sexual
1017 desire, performance, and satisfaction are difficult to obtain, however, in part because patients and
1018 physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of
1019 untoward sexual experience and performance cited in product labeling, are likely to
1020 underestimate their actual incidence.

1021 In placebo-controlled clinical trials involving more than 3,200 patients, the ranges for the
1022 reported incidence of sexual side effects in males and females with major depressive disorder,
1023 OCD, panic disorder, social anxiety disorder, GAD, and PTSD are displayed in Table 5.

1024

1025 **Table 5. 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%

1026
 1027 There are no adequate and well-controlled studies examining sexual dysfunction with
 1028 paroxetine treatment.

1029 Paroxetine treatment has been associated with several cases of priapism. In those cases with a
 1030 known outcome, patients recovered without sequelae.

1031 While it is difficult to know the precise risk of sexual dysfunction associated with the use of
 1032 SSRIs, physicians should routinely inquire about such possible side effects.

1033 **Weight and Vital Sign Changes:** Significant weight loss may be an undesirable result of
 1034 treatment with PAXIL for some patients but, on average, patients in controlled trials had minimal
 1035 (about 1 pound) weight loss versus smaller changes on placebo and active control. No significant
 1036 changes in vital signs (systolic and diastolic blood pressure, pulse and temperature) were
 1037 observed in patients treated with PAXIL in controlled clinical trials.

1038 **ECG Changes:** In an analysis of ECGs obtained in 682 patients treated with PAXIL and
 1039 415 patients treated with placebo in controlled clinical trials, no clinically significant changes
 1040 were seen in the ECGs of either group.

1041 **Liver Function Tests:** In placebo-controlled clinical trials, patients treated with PAXIL
 1042 exhibited abnormal values on liver function tests at no greater rate than that seen in
 1043 placebo-treated patients. In particular, the PAXIL-versus-placebo comparisons for alkaline
 1044 phosphatase, SGOT, SGPT, and bilirubin revealed no differences in the percentage of patients
 1045 with marked abnormalities.

1046 **Hallucinations:** In pooled clinical trials of immediate-release paroxetine hydrochloride,
 1047 hallucinations were observed in 22 of 9089 patients receiving drug and 4 of 3187 patients
 1048 receiving placebo.

1049 **Other Events Observed During the Premarketing Evaluation of PAXIL:** During its
 1050 premarketing assessment in major depressive disorder, multiple doses of PAXIL were
 1051 administered to 6,145 patients in phase 2 and 3 studies. The conditions and duration of exposure
 1052 to PAXIL varied greatly and included (in overlapping categories) open and double-blind studies,
 1053 uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose, and titration
 1054 studies. During premarketing clinical trials in OCD, panic disorder, social anxiety disorder,
 1055 generalized anxiety disorder, and posttraumatic stress disorder, 542, 469, 522, 735, and 676
 1056 patients, respectively, received multiple doses of PAXIL. Untoward events associated with this
 1057 exposure were recorded by clinical investigators using terminology of their own choosing.

1058 Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals
1059 experiencing adverse events without first grouping similar types of untoward events into a
1060 smaller number of standardized event categories.

1061 In the tabulations that follow, reported adverse events were classified using a standard
1062 COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the
1063 proportion of the 9,089 patients exposed to multiple doses of PAXIL who experienced an event
1064 of the type cited on at least 1 occasion while receiving PAXIL. All reported events are included
1065 except those already listed in Tables 1 to 3, those reported in terms so general as to be
1066 uninformative and those events where a drug cause was remote. It is important to emphasize that
1067 although the events reported occurred during treatment with paroxetine, they were not
1068 necessarily caused by it.

1069 Events are further categorized by body system and listed in order of decreasing frequency
1070 according to the following definitions: Frequent adverse events are those occurring on 1 or more
1071 occasions in at least 1/100 patients (only those not already listed in the tabulated results from
1072 placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in
1073 1/100 to 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients. Events
1074 of major clinical importance are also described in the PRECAUTIONS section.

1075 **Body as a Whole:** *Infrequent:* Allergic reaction, chills, face edema, malaise, neck pain;
1076 *rare:* Adrenergic syndrome, cellulitis, moniliasis, neck rigidity, pelvic pain, peritonitis, sepsis,
1077 ulcer.

1078 **Cardiovascular System:** *Frequent:* Hypertension, tachycardia; *infrequent:* Bradycardia,
1079 hematoma, hypotension, migraine, syncope; *rare:* Angina pectoris, arrhythmia nodal, atrial
1080 fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart
1081 failure, heart block, low cardiac output, myocardial infarct, myocardial ischemia, pallor,
1082 phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis,
1083 varicose vein, vascular headache, ventricular extrasystoles.

1084 **Digestive System:** *Infrequent:* Bruxism, colitis, dysphagia, eructation, gastritis,
1085 gastroenteritis, gingivitis, glossitis, increased salivation, liver function tests abnormal, rectal
1086 hemorrhage, ulcerative stomatitis; *rare:* Aphthous stomatitis, bloody diarrhea, bulimia,
1087 cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal
1088 incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, intestinal obstruction,
1089 jaundice, melena, mouth ulceration, peptic ulcer, salivary gland enlargement, sialadenitis,
1090 stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries.

1091 **Endocrine System:** *Rare:* Diabetes mellitus, goiter, hyperthyroidism, hypothyroidism,
1092 thyroiditis.

1093 **Hemic and Lymphatic Systems:** *Infrequent:* Anemia, leukopenia, lymphadenopathy,
1094 purpura; *rare:* Abnormal erythrocytes, basophilia, bleeding time increased, eosinophilia,
1095 hypochromic anemia, iron deficiency anemia, leukocytosis, lymphedema, abnormal
1096 lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia,
1097 thrombocythemia, thrombocytopenia.

1098 **Metabolic and Nutritional:** *Frequent:* Weight gain; *infrequent:* Edema, peripheral edema,
1099 SGOT increased, SGPT increased, thirst, weight loss; *rare:* Alkaline phosphatase increased,
1100 bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, gamma
1101 globulins increased, gout, hypercalcemia, hypercholesteremia, hyperglycemia, hyperkalemia,
1102 hyperphosphatemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, ketosis, lactic
1103 dehydrogenase increased, non-protein nitrogen (NPN) increased.

1104 **Musculoskeletal System:** *Frequent:* Arthralgia; *infrequent:* Arthritis, arthrosis; *rare:*
1105 Bursitis, myositis, osteoporosis, generalized spasm, tenosynovitis, tetany.

1106 **Nervous System:** *Frequent:* Emotional lability, vertigo; *infrequent:* Abnormal thinking,
1107 alcohol abuse, ataxia, dystonia, dyskinesia, euphoria, hallucinations, hostility, hypertonia,
1108 hypesthesia, hypokinesia, incoordination, lack of emotion, libido increased, manic reaction,
1109 neurosis, paralysis, paranoid reaction; *rare:* Abnormal gait, akinesia, antisocial reaction, aphasia,
1110 choreoathetosis, circumoral paresthesias, convulsion, delirium, delusions, diplopia, drug
1111 dependence, dysarthria, extrapyramidal syndrome, fasciculations, grand mal convulsion,
1112 hyperalgesia, hysteria, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy,
1113 nystagmus, peripheral neuritis, psychotic depression, psychosis, reflexes decreased, reflexes
1114 increased, stupor, torticollis, trismus, withdrawal syndrome.

1115 **Respiratory System:** *Infrequent:* Asthma, bronchitis, dyspnea, epistaxis, hyperventilation,
1116 pneumonia, respiratory flu; *rare:* Emphysema, hemoptysis, hiccups, lung fibrosis, pulmonary
1117 edema, sputum increased, stridor, voice alteration.

1118 **Skin and Appendages:** *Frequent:* Pruritus; *infrequent:* Acne, alopecia, contact dermatitis,
1119 dry skin, ecchymosis, eczema, herpes simplex, photosensitivity, urticaria; *rare:* Angioedema,
1120 erythema nodosum, erythema multiforme, exfoliative dermatitis, fungal dermatitis, furunculosis;
1121 herpes zoster, hirsutism, maculopapular rash, seborrhea, skin discoloration, skin hypertrophy,
1122 skin ulcer, sweating decreased, vesiculobullous rash.

1123 **Special Senses:** *Frequent:* Tinnitus; *infrequent:* Abnormality of accommodation,
1124 conjunctivitis, ear pain, eye pain, keratoconjunctivitis, mydriasis, otitis media; *rare:* Amblyopia,
1125 anisocoria, blepharitis, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, eye
1126 hemorrhage, glaucoma, hyperacusis, night blindness, otitis externa, parosmia, photophobia,
1127 ptosis, retinal hemorrhage, taste loss, visual field defect.

1128 **Urogenital System:** *Infrequent:* Amenorrhea, breast pain, cystitis, dysuria, hematuria,
1129 menorrhagia, nocturia, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency,
1130 vaginitis; *rare:* Abortion, breast atrophy, breast enlargement, endometrial disorder, epididymitis,
1131 female lactation, fibrocystic breast, kidney calculus, kidney pain, leukorrhea, mastitis,
1132 metrorrhagia, nephritis, oliguria, salpingitis, urethritis, urinary casts, uterine spasm, urolith,
1133 vaginal hemorrhage, vaginal moniliasis.

1134 **Postmarketing Reports:** Voluntary reports of adverse events in patients taking PAXIL that
1135 have been received since market introduction and not listed above that may have no causal
1136 relationship with the drug include acute pancreatitis, elevated liver function tests (the most
1137 severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated

1138 with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism,
1139 syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and
1140 galactorrhea, neuroleptic malignant syndrome–like events, serotonin syndrome; extrapyramidal
1141 symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia,
1142 oculogyric crisis which has been associated with concomitant use of pimozide; tremor and
1143 trismus; status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis,
1144 anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular
1145 tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, events related
1146 to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and
1147 agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura). There has been
1148 a case report of an elevated phenytoin level after 4 weeks of PAXIL and phenytoin
1149 coadministration. There has been a case report of severe hypotension when PAXIL was added to
1150 chronic metoprolol treatment.

1151 **DRUG ABUSE AND DEPENDENCE**

1152 **Controlled Substance Class:** PAXIL is not a controlled substance.

1153 **Physical and Psychologic Dependence:** PAXIL has not been systematically studied in
1154 animals or humans for its potential for abuse, tolerance or physical dependence. While the
1155 clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were
1156 not systematic and it is not possible to predict on the basis of this limited experience the extent to
1157 which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently,
1158 patients should be evaluated carefully for history of drug abuse, and such patients should be
1159 observed closely for signs of misuse or abuse of PAXIL (e.g., development of tolerance,
1160 incrementations of dose, drug-seeking behavior).

1161 **OVERDOSAGE**

1162 **Human Experience:** Since the introduction of PAXIL in the United States, 342 spontaneous
1163 cases of deliberate or accidental overdosage during paroxetine treatment have been reported
1164 worldwide (circa 1999). These include overdoses with paroxetine alone and in combination with
1165 other substances. Of these, 48 cases were fatal and of the fatalities, 17 appeared to involve
1166 paroxetine alone. Eight fatal cases that documented the amount of paroxetine ingested were
1167 generally confounded by the ingestion of other drugs or alcohol or the presence of significant
1168 comorbid conditions. Of 145 non-fatal cases with known outcome, most recovered without
1169 sequelae. The largest known ingestion involved 2,000 mg of paroxetine (33 times the maximum
1170 recommended daily dose) in a patient who recovered.

1171 Commonly reported adverse events associated with paroxetine overdosage include
1172 somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other
1173 notable signs and symptoms observed with overdoses involving paroxetine (alone or with other
1174 substances) include mydriasis, convulsions (including status epilepticus), ventricular
1175 dysrhythmias (including torsade de pointes), hypertension, aggressive reactions, syncope,
1176 hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction

1177 (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin
1178 syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

1179 **Overdosage Management:** Treatment should consist of those general measures employed in
1180 the management of overdosage with any drugs effective in the treatment of major depressive
1181 disorder.

1182 Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital
1183 signs. General supportive and symptomatic measures are also recommended. Induction of emesis
1184 is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway
1185 protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic
1186 patients.

1187 Activated charcoal should be administered. Due to the large volume of distribution of this
1188 drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of
1189 benefit. No specific antidotes for paroxetine are known.

1190 A specific caution involves patients who are taking or have recently taken paroxetine who
1191 might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the
1192 parent tricyclic and/or an active metabolite may increase the possibility of clinically significant
1193 sequelae and extend the time needed for close medical observation (see PRECAUTIONS—
1194 *Drugs Metabolized by Cytochrome CYP2D6*).

1195 In managing overdosage, consider the possibility of multiple drug involvement. The physician
1196 should consider contacting a poison control center for additional information on the treatment of
1197 any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians'*
1198 *Desk Reference* (PDR).

1199 **DOSAGE AND ADMINISTRATION**

1200 **Major Depressive Disorder: Usual Initial Dosage:** PAXIL should be administered as a
1201 single daily dose with or without food, usually in the morning. The recommended initial dose is
1202 20 mg/day. Patients were dosed in a range of 20 to 50 mg/day in the clinical trials demonstrating
1203 the effectiveness of PAXIL in the treatment of major depressive disorder. As with all drugs
1204 effective in the treatment of major depressive disorder, the full effect may be delayed. Some
1205 patients not responding to a 20-mg dose may benefit from dose increases, in 10-mg/day
1206 increments, up to a maximum of 50 mg/day. Dose changes should occur at intervals of at least
1207 1 week.

1208 **Maintenance Therapy:** There is no body of evidence available to answer the question of
1209 how long the patient treated with PAXIL should remain on it. It is generally agreed that acute
1210 episodes of major depressive disorder require several months or longer of sustained
1211 pharmacologic therapy. Whether the dose needed to induce remission is identical to the dose
1212 needed to maintain and/or sustain euthymia is unknown.

1213 Systematic evaluation of the efficacy of PAXIL has shown that efficacy is maintained for
1214 periods of up to 1 year with doses that averaged about 30 mg.

1215 **Obsessive Compulsive Disorder: Usual Initial Dosage:** PAXIL should be administered
1216 as a single daily dose with or without food, usually in the morning. The recommended dose of
1217 PAXIL in the treatment of OCD is 40 mg daily. Patients should be started on 20 mg/day and the
1218 dose can be increased in 10-mg/day increments. Dose changes should occur at intervals of at
1219 least 1 week. Patients were dosed in a range of 20 to 60 mg/day in the clinical trials
1220 demonstrating the effectiveness of PAXIL in the treatment of OCD. The maximum dosage
1221 should not exceed 60 mg/day.

1222 **Maintenance Therapy:** Long-term maintenance of efficacy was demonstrated in a 6-month
1223 relapse prevention trial. In this trial, patients with OCD assigned to paroxetine demonstrated a
1224 lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY—
1225 Clinical Trials). OCD is a chronic condition, and it is reasonable to consider continuation for a
1226 responding patient. Dosage adjustments should be made to maintain the patient on the lowest
1227 effective dosage, and patients should be periodically reassessed to determine the need for
1228 continued treatment.

1229 **Panic Disorder: Usual Initial Dosage:** PAXIL should be administered as a single daily dose
1230 with or without food, usually in the morning. The target dose of PAXIL in the treatment of panic
1231 disorder is 40 mg/day. Patients should be started on 10 mg/day. Dose changes should occur in
1232 10-mg/day increments and at intervals of at least 1 week. Patients were dosed in a range of 10 to
1233 60 mg/day in the clinical trials demonstrating the effectiveness of PAXIL. The maximum dosage
1234 should not exceed 60 mg/day.

1235 **Maintenance Therapy:** Long-term maintenance of efficacy was demonstrated in a 3-month
1236 relapse prevention trial. In this trial, patients with panic disorder assigned to paroxetine
1237 demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL
1238 PHARMACOLOGY—Clinical Trials). Panic disorder is a chronic condition, and it is reasonable
1239 to consider continuation for a responding patient. Dosage adjustments should be made to
1240 maintain the patient on the lowest effective dosage, and patients should be periodically
1241 reassessed to determine the need for continued treatment.

1242 **Social Anxiety Disorder: Usual Initial Dosage:** PAXIL should be administered as a single
1243 daily dose with or without food, usually in the morning. The recommended and initial dosage is
1244 20 mg/day. In clinical trials the effectiveness of PAXIL was demonstrated in patients dosed in a
1245 range of 20 to 60 mg/day. While the safety of PAXIL has been evaluated in patients with social
1246 anxiety disorder at doses up to 60 mg/day, available information does not suggest any additional
1247 benefit for doses above 20 mg/day (see CLINICAL PHARMACOLOGY—Clinical Trials).

1248 **Maintenance Therapy:** There is no body of evidence available to answer the question of
1249 how long the patient treated with PAXIL should remain on it. Although the efficacy of PAXIL
1250 beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials, social anxiety
1251 disorder is recognized as a chronic condition, and it is reasonable to consider continuation of
1252 treatment for a responding patient. Dosage adjustments should be made to maintain the patient
1253 on the lowest effective dosage, and patients should be periodically reassessed to determine the
1254 need for continued treatment.

1255 **Generalized Anxiety Disorder: Usual Initial Dosage:** PAXIL should be administered as a
1256 single daily dose with or without food, usually in the morning. In clinical trials the effectiveness
1257 of PAXIL was demonstrated in patients dosed in a range of 20 to 50 mg/day. The recommended
1258 starting dosage and the established effective dosage is 20 mg/day. There is not sufficient
1259 evidence to suggest a greater benefit to doses higher than 20 mg/day. Dose changes should occur
1260 in 10 mg/day increments and at intervals of at least 1 week.

1261 **Maintenance Therapy:** Systematic evaluation of continuing PAXIL for periods of up to
1262 24 weeks in patients with Generalized Anxiety Disorder who had responded while taking PAXIL
1263 during an 8-week acute treatment phase has demonstrated a benefit of such maintenance (see
1264 CLINICAL PHARMACOLOGY—Clinical Trials). Nevertheless, patients should be periodically
1265 reassessed to determine the need for maintenance treatment.

1266 **Posttraumatic Stress Disorder: Usual Initial Dosage:** PAXIL should be administered as
1267 a single daily dose with or without food, usually in the morning. The recommended starting
1268 dosage and the established effective dosage is 20 mg/day. In 1 clinical trial, the effectiveness of
1269 PAXIL was demonstrated in patients dosed in a range of 20 to 50 mg/day. However, in a fixed
1270 dose study, there was not sufficient evidence to suggest a greater benefit for a dose of 40 mg/day
1271 compared to 20 mg/day. Dose changes, if indicated, should occur in 10 mg/day increments and at
1272 intervals of at least 1 week.

1273 **Maintenance Therapy:** There is no body of evidence available to answer the question of
1274 how long the patient treated with PAXIL should remain on it. Although the efficacy of PAXIL
1275 beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials, PTSD is
1276 recognized as a chronic condition, and it is reasonable to consider continuation of treatment for a
1277 responding patient. Dosage adjustments should be made to maintain the patient on the lowest
1278 effective dosage, and patients should be periodically reassessed to determine the need for
1279 continued treatment.

1280 **Special Populations: Treatment of Pregnant Women During the Third Trimester:**
1281 Neonates exposed to PAXIL and other SSRIs or SNRIs, late in the third trimester have
1282 developed complications requiring prolonged hospitalization, respiratory support, and tube
1283 feeding (see WARNINGS). When treating pregnant women with paroxetine during the third
1284 trimester, the physician should carefully consider the potential risks and benefits of treatment.
1285 The physician may consider tapering paroxetine in the third trimester.

1286 **Dosage for Elderly or Debilitated Patients, and Patients With Severe Renal or
1287 Hepatic Impairment:** The recommended initial dose is 10 mg/day for elderly patients,
1288 debilitated patients, and/or patients with severe renal or hepatic impairment. Increases may be
1289 made if indicated. Dosage should not exceed 40 mg/day.

1290 **Switching Patients to or From a Monoamine Oxidase Inhibitor:** At least 14 days
1291 should elapse between discontinuation of an MAOI and initiation of therapy with PAXIL.
1292 Similarly, at least 14 days should be allowed after stopping PAXIL before starting an MAOI.

1293 **Discontinuation of Treatment With PAXIL:** Symptoms associated with discontinuation of
1294 PAXIL have been reported (see PRECAUTIONS). Patients should be monitored for these

1295 symptoms when discontinuing treatment, regardless of the indication for which PAXIL is being
1296 prescribed. A gradual reduction in the dose rather than abrupt cessation is recommended
1297 whenever possible. If intolerable symptoms occur following a decrease in the dose or upon
1298 discontinuation of treatment, then resuming the previously prescribed dose may be considered.
1299 Subsequently, the physician may continue decreasing the dose but at a more gradual rate.
1300 **NOTE: SHAKE SUSPENSION WELL BEFORE USING.**

1301 **HOW SUPPLIED**

1302 **Tablets:** Film-coated, modified-oval as follows:
1303 10-mg yellow, scored tablets engraved on the front with PAXIL and on the back with 10.
1304 NDC 0029-3210-13 Bottles of 30
1305 20-mg pink, scored tablets engraved on the front with PAXIL and on the back with 20.
1306 NDC 0029-3211-13 Bottles of 30
1307 NDC 0029-3211-59 Bottles of 90
1308 NDC 0029-3211-21 SUP 100s (intended for institutional use only)
1309 30-mg blue tablets engraved on the front with PAXIL and on the back with 30.
1310 NDC 0029-3212-13 Bottles of 30
1311 40-mg green tablets engraved on the front with PAXIL and on the back with 40.
1312 NDC 0029-3213-13 Bottles of 30
1313 Store tablets between 15° and 30°C (59° and 86°F).
1314 **Oral Suspension:** Orange-colored, orange-flavored, 10 mg/5 mL, in 250 mL white bottles.
1315 NDC 0029-3215-48
1316 Store suspension at or below 25°C (77°F).
1317 PAXIL is a registered trademark of GlaxoSmithKline.
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Medication Guide

**PAXIL® (PAX-il) (paroxetine hydrochloride) Tablets and Oral Suspension
About Using Antidepressants in Children and Teenagers**

What is the most important information I should know if my child is being prescribed an antidepressant?

Parents or guardians need to think about 4 important things when their child is prescribed an antidepressant:

1. There is a risk of suicidal thoughts or actions
2. How to try to prevent suicidal thoughts or actions in your child
3. You should watch for certain signs if your child is taking an antidepressant
4. There are benefits and risks when using antidepressants

1334 **1. There is a Risk of Suicidal Thoughts or Actions**

1335
1336 Children and teenagers sometimes think about suicide, and many report trying to kill themselves.

1337
1338 Antidepressants increase suicidal thoughts and actions in some children and teenagers. But
1339 suicidal thoughts and actions can also be caused by depression, a serious medical condition that
1340 is commonly treated with antidepressants. Thinking about killing yourself or trying to kill
1341 yourself is called *suicidality* or *being suicidal*.

1342
1343 A large study combined the results of 24 different studies of children and teenagers with
1344 depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an
1345 antidepressant for 1 to 4 months. ***No one committed suicide in these studies***, but some patients
1346 became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4
1347 out of every 100 patients became suicidal.

1348
1349 **For some children and teenagers, the risks of suicidal actions may be especially high.** These
1350 include patients with

- 1351 • Bipolar illness (sometimes called manic-depressive illness)
- 1352 • A family history of bipolar illness
- 1353 • A personal or family history of attempting suicide

1354 If any of these are present, make sure you tell your healthcare provider before your child takes an
1355 antidepressant.

1356
1357 **2. How to Try to Prevent Suicidal Thoughts and Actions**

1358
1359 To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her
1360 or his moods or actions, especially if the changes occur suddenly. Other important people in your
1361 child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers,
1362 and other important people). The changes to look out for are listed in Section 3, on what to watch
1363 for.

1364
1365 Whenever an antidepressant is started or its dose is changed, pay close attention to your child.
1366 After starting an antidepressant, your child should generally see his or her healthcare provider:

- 1367 • Once a week for the first 4 weeks
- 1368 • Every 2 weeks for the next 4 weeks
- 1369 • After taking the antidepressant for 12 weeks
- 1370 • After 12 weeks, follow your healthcare provider's advice about how often to come back
- 1371 • More often if problems or questions arise (see Section 3)

1372
1373 You should call your child's healthcare provider between visits if needed.

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3. You Should Watch for Certain Signs If Your Child is Taking an Antidepressant

Contact your child’s healthcare provider *right away* if your child exhibits any of the following signs for the first time, or if they seem worse, or worry you, your child, or your child’s teacher:

- Thoughts about suicide or dying
- Attempts to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Difficulty sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking
- Other unusual changes in behavior or mood

Never let your child stop taking an antidepressant without first talking to his or her healthcare provider. Stopping an antidepressant suddenly can cause other symptoms.

4. There are Benefits and Risks When Using Antidepressants

Antidepressants are used to treat depression and other illnesses. Depression and other illnesses can lead to suicide. In some children and teenagers, treatment with an antidepressant increases suicidal thinking or actions. It is important to discuss all the risks of treating depression and also the risks of not treating it. You and your child should discuss all treatment choices with your healthcare provider, not just the use of antidepressants.

Other side effects can occur with antidepressants (see section below).

Of all the antidepressants, only fluoxetine (Prozac®)* has been FDA approved to treat pediatric depression.

For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine (Prozac®)*, sertraline (Zoloft®)*, fluvoxamine, and clomipramine (Anafranil®)*.

Your healthcare provider may suggest other antidepressants based on the past experience of your child or other family members.

1414 **Is this all I need to know if my child is being prescribed an antidepressant?**

1415

1416 No. This is a warning about the risk for suicidality. Other side effects can occur with
1417 antidepressants. Be sure to ask your healthcare provider to explain all the side effects of the
1418 particular drug he or she is prescribing. Also ask about drugs to avoid when taking an
1419 antidepressant. Ask your healthcare provider or pharmacist where to find more information.

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1422 *The following are registered trademarks of their respective manufacturers: Prozac[®]/Eli Lilly
1423 and Company; Zoloft[®]/Pfizer Pharmaceuticals; Anafranil[®]/Mallinckrodt Inc.

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1426 This Medication Guide has been approved by the U.S. Food and Drug Administration for all
1427 antidepressants.

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