

1 PRESCRIBING INFORMATION

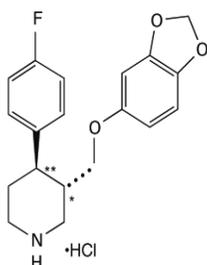
2 **PAXIL[®]**
3 **(paroxetine hydrochloride)**
4 **Tablets and Oral Suspension**
5

6 **Suicidality and Antidepressant Drugs**

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

21 **DESCRIPTION**

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



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

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

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

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

41 **CLINICAL PHARMACOLOGY**

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

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

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

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

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

73 and C_{\min} values were about 6 and 14 times what would be predicted from single-dose studies.
74 Steady-state drug exposure based on AUC_{0-24} was about 8 times greater than would have been
75 predicted from single-dose data in these subjects. The excess accumulation is a consequence of
76 the fact that 1 of the enzymes that metabolizes paroxetine is readily saturable.

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

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

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

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

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

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

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

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

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

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

124 **Clinical Trials**

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

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

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

152 The following table provides the outcome classification by treatment group on Global
 153 Improvement items of the Clinical Global Impression (CGI) scale for Study 1.
 154

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%

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

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

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

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

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

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

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

183 Long-term maintenance effects of PAXIL in panic disorder were demonstrated in an

184 extension to Study 1. Patients who were responders during the 10-week double-blind phase and
185 during a 3-month double-blind extension phase were randomized to either paroxetine (10, 20, or
186 40 mg/day) or placebo in a 3-month double-blind relapse prevention phase. Patients randomized
187 to paroxetine were significantly less likely to relapse than comparably treated patients who were
188 randomized to placebo.

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

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

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

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

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

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

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

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

224 placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score, the primary outcome.

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

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

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

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

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

258 A third study, also a flexible-dose study comparing paroxetine (20 to 50 mg daily) to placebo,
259 demonstrated PAXIL to be significantly superior to placebo on change from baseline for CAPS-
260 2 total score, but not on proportion of responders on the CGI-I.

261 The majority of patients in these trials were women (68% women: 377 out of 551 subjects in
262 Study 1 and 66% women: 202 out of 303 subjects in Study 2). Subgroup analyses did not
263 indicate differences in treatment outcomes as a function of gender. There were an insufficient

264 number of patients who were 65 years and older or were non-Caucasian to conduct subgroup
265 analyses on the basis of age or race, respectively.

266 **INDICATIONS AND USAGE**

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

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

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

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

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

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

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

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

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

303 the attacks.

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

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

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

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

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

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

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

342 The efficacy of PAXIL in the treatment of GAD was established in two 8-week

343 placebo-controlled trials in adults with GAD. PAXIL has not been studied in children or
344 adolescents with Generalized Anxiety Disorder (see CLINICAL PHARMACOLOGY: Clinical
345 Trials).

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

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

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

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

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

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

380 **CONTRAINDICATIONS**

381 Concomitant use in patients taking either monoamine oxidase inhibitors (MAOIs), including

382 linezolid, an antibiotic which is a reversible non-selective MAOI, or thioridazine is
383 contraindicated (see WARNINGS and PRECAUTIONS).

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

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

387 **WARNINGS**

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

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

413

414 **Table 1**

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 Patients Treated
Increases Compared to Placebo	
<18	14 additional cases
18-24	5 additional cases
Decreases Compared to Placebo	
25-64	1 fewer case
≥65	6 fewer cases

415

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

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

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

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

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

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

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

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

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

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

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

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

488 **The concomitant use of PAXIL with MAOIs intended to treat depression is**
489 **contraindicated.**

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

493 **The concomitant use of PAXIL with serotonin precursors (such as tryptophan) is not**
494 **recommended.**

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

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

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

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

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

525 A separate retrospective cohort study using US United Healthcare data evaluated 5,956 infants

526 of mothers dispensed paroxetine or other antidepressants during the first trimester (n = 815 for
527 paroxetine). This study showed a trend towards an increased risk for cardiovascular
528 malformations for paroxetine compared to other antidepressants (OR 1.5; 95% confidence
529 interval 0.8-2.9). The prevalence of cardiovascular malformations following first trimester
530 dispensing was 1.5% for paroxetine vs. 1% for other antidepressants. Nine out of 12 infants with
531 cardiovascular malformations whose mothers were dispensed paroxetine in the first trimester had
532 VSDs. This study also suggested an increased risk of overall major congenital malformations
533 (inclusive of the cardiovascular defects) for paroxetine compared to other antidepressants (OR
534 1.8; 95% confidence interval 1.2-2.8). The prevalence of all congenital malformations following
535 first trimester exposure was 4% for paroxetine vs. 2% for other antidepressants.

536 **Animal Findings:** Reproduction studies were performed at doses up to 50 mg/kg/day in rats
537 and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately
538 8 (rat) and 2 (rabbit) times the maximum recommended human dose (MRHD) on an mg/m²
539 basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was
540 an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last
541 trimester of gestation and continued throughout lactation. This effect occurred at a dose of
542 1 mg/kg/day or approximately one-sixth of the MRHD on an mg/m² basis. The no-effect dose for
543 rat pup mortality was not determined. The cause of these deaths is not known.

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

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

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

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

572 **PRECAUTIONS**

573 **General: Activation of Mania/Hypomania:** During premarketing testing, hypomania or
574 mania occurred in approximately 1.0% of unipolar patients treated with PAXIL compared to
575 1.1% of active-control and 0.3% of placebo-treated unipolar patients. In a subset of patients
576 classified as bipolar, the rate of manic episodes was 2.2% for PAXIL and 11.6% for the
577 combined active-control groups. As with all drugs effective in the treatment of major depressive
578 disorder, PAXIL should be used cautiously in patients with a history of mania.

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

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

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

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

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

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

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

611 **Hyponatremia:** Hyponatremia may occur as a result of treatment with SSRIs and SNRIs,
612 including PAXIL. In many cases, this hyponatremia appears to be the result of the syndrome of
613 inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than
614 110 mmol/L have been reported. Elderly patients may be at greater risk of developing
615 hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise
616 volume depleted may be at greater risk (see PRECAUTIONS: Geriatric Use). Discontinuation of
617 PAXIL should be considered in patients with symptomatic hyponatremia and appropriate
618 medical intervention should be instituted.

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

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

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

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

642 As with other SSRIs, mydriasis has been infrequently reported in premarketing studies with
643 PAXIL. A few cases of acute angle closure glaucoma associated with paroxetine therapy have
644 been reported in the literature. As mydriasis can cause acute angle closure in patients with

645 narrow angle glaucoma, caution should be used when PAXIL is prescribed for patients with
646 narrow angle glaucoma.

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

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

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

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

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

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

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

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

684 Patients should be cautioned about the concomitant use of paroxetine and NSAIDs, aspirin,

685 warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that
686 interfere with serotonin reuptake and these agents has been associated with an increased risk of
687 bleeding.

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

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

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

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

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

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

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

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

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

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

720 **Serotonergic Drugs:** Based on the mechanism of action of SNRIs and SSRIs, including
721 paroxetine hydrochloride, and the potential for serotonin syndrome, caution is advised when
722 PAXIL is coadministered with other drugs that may affect the serotonergic neurotransmitter
723 systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI),
724 lithium, fentanyl, tramadol, or St. John's Wort (see WARNINGS: Serotonin Syndrome or

725 Neuroleptic Malignant Syndrome (NMS)-like Reactions). The concomitant use of PAXIL with
726 MAOIs (including linezolid) is contraindicated (see CONTRAINDICATIONS). The
727 concomitant use of PAXIL with other SSRIs, SNRIs or tryptophan is not recommended (see
728 PRECAUTIONS: Drug Interactions *Tryptophan*).

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

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

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

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

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

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

758 **Phenytoin:** When a single oral 30-mg dose of PAXIL was administered at phenytoin steady
759 state (300 mg once daily for 14 days), paroxetine AUC and T_{1/2} were reduced (by an average of
760 50% and 35%, respectively) compared to PAXIL administered alone. In a separate study, when a
761 single oral 300-mg dose of phenytoin was administered at paroxetine steady state (30 mg once
762 daily for 14 days), phenytoin AUC was slightly reduced (12% on average) compared to
763 phenytoin administered alone. Since both drugs exhibit nonlinear pharmacokinetics, the above
764 studies may not address the case where the 2 drugs are both being chronically dosed. No initial

765 dosage adjustments are considered necessary when these drugs are coadministered; any
766 subsequent adjustments should be guided by clinical effect (see ADVERSE REACTIONS:
767 Postmarketing Reports).

768 **Drugs Metabolized by CYP2D6:** Many drugs, including most drugs effective in the
769 treatment of major depressive disorder (paroxetine, other SSRIs and many tricyclics), are
770 metabolized by the cytochrome P₄₅₀ isozyme CYP2D6. Like other agents that are metabolized by
771 CYP2D6, paroxetine may significantly inhibit the activity of this isozyme. In most patients
772 (>90%), this CYP2D6 isozyme is saturated early during dosing with PAXIL. In 1 study, daily
773 dosing of PAXIL (20 mg once daily) under steady-state conditions increased single dose
774 desipramine (100 mg) C_{max}, AUC, and T_{1/2} by an average of approximately 2-, 5-, and 3-fold,
775 respectively. Concomitant use of paroxetine with risperidone, a CYP2D6 substrate has also been
776 evaluated. In 1 study, daily dosing of paroxetine 20 mg in patients stabilized on risperidone (4 to
777 8 mg/day) increased mean plasma concentrations of risperidone approximately 4-fold, decreased
778 9-hydroxyrisperidone concentrations approximately 10%, and increased concentrations of the
779 active moiety (the sum of risperidone plus 9-hydroxyrisperidone) approximately 1.4-fold. The
780 effect of paroxetine on the pharmacokinetics of atomoxetine has been evaluated when both drugs
781 were at steady state. In healthy volunteers who were extensive metabolizers of CYP2D6,
782 paroxetine 20 mg daily was given in combination with 20 mg atomoxetine every 12 hours. This
783 resulted in increases in steady state atomoxetine AUC values that were 6- to 8-fold greater and in
784 atomoxetine C_{max} values that were 3- to 4-fold greater than when atomoxetine was given alone.
785 Dosage adjustment of atomoxetine may be necessary and it is recommended that atomoxetine be
786 initiated at a reduced dose when it is given with paroxetine.

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

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

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

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

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

804 **Drugs Metabolized by Cytochrome CYP3A4:** An in vivo interaction study involving

805 the coadministration under steady-state conditions of paroxetine and terfenadine, a substrate for
806 cytochrome CYP3A4, revealed no effect of paroxetine on terfenadine pharmacokinetics. In
807 addition, in vitro studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be
808 at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several
809 substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam, and
810 cyclosporine. Based on the assumption that the relationship between paroxetine's in vitro K_i and
811 its lack of effect on terfenadine's in vivo clearance predicts its effect on other CYP3A4
812 substrates, paroxetine's extent of inhibition of CYP3A4 activity is not likely to be of clinical
813 significance.

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

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

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

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

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

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

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

843 **Procyclidine:** Daily oral dosing of PAXIL (30 mg once daily) increased steady-state AUC_{0-24} , C_{max} , and C_{min} values of procyclidine (5 mg oral once daily) by 35%, 37%, and 67%,
844

845 respectively, compared to procyclidine alone at steady state. If anticholinergic effects are seen,
846 the dose of procyclidine should be reduced.

847 **Beta-Blockers:** In a study where propranolol (80 mg twice daily) was dosed orally for
848 18 days, the established steady-state plasma concentrations of propranolol were unaltered during
849 coadministration with PAXIL (30 mg once daily) for the final 10 days. The effects of
850 propranolol on paroxetine have not been evaluated (see ADVERSE REACTIONS:
851 Postmarketing Reports).

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

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

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

861 **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** Two-year
862 carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and
863 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to 2.4 (mouse) and
864 3.9 (rat) times the MRHD for major depressive disorder, social anxiety disorder, GAD, and
865 PTSD on a mg/m² basis. Because the MRHD for major depressive disorder is slightly less than
866 that for OCD (50 mg versus 60 mg), the doses used in these carcinogenicity studies were only
867 2.0 (mouse) and 3.2 (rat) times the MRHD for OCD. There was a significantly greater number of
868 male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50, and 4/50 for
869 control, low-, middle-, and high-dose groups, respectively) and a significantly increased linear
870 trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats
871 were not affected. Although there was a dose-related increase in the number of tumors in mice,
872 there was no drug-related increase in the number of mice with tumors. The relevance of these
873 findings to humans is unknown.

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

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

880 A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of
881 15 mg/kg/day, which is 2.9 times the MRHD for major depressive disorder, social anxiety
882 disorder, GAD, and PTSD or 2.4 times the MRHD for OCD on a mg/m² basis. Irreversible
883 lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to
884 52 weeks. These lesions consisted of vacuolation of epididymal tubular epithelium at

885 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with arrested
886 spermatogenesis at 25 mg/kg/day (9.8 and 4.9 times the MRHD for major depressive disorder,
887 social anxiety disorder, and GAD; 8.2 and 4.1 times the MRHD for OCD and PD on a mg/m²
888 basis).

889 **Pregnancy:** Pregnancy Category D. See WARNINGS: Usage in Pregnancy: *Teratogenic*
890 *Effects* and *Nonteratogenic Effects*.

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

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

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

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

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

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

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

919 **ADVERSE REACTIONS**

920 **Associated With Discontinuation of Treatment:** Twenty percent (1,199/6,145) of patients
921 treated with PAXIL in worldwide clinical trials in major depressive disorder and 16.1%
922 (84/522), 11.8% (64/542), 9.4% (44/469), 10.7% (79/735), and 11.7% (79/676) of patients
923 treated with PAXIL in worldwide trials in social anxiety disorder, OCD, panic disorder, GAD,

924 and PTSD, respectively, discontinued treatment due to an adverse event. The most common
 925 events ($\geq 1\%$) associated with discontinuation and considered to be drug related (i.e., those events
 926 associated with dropout at a rate approximately twice or greater for PAXIL compared to placebo)
 927 included the following:
 928

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

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

931 a. Incidence corrected for gender.

932
 933 **Commonly Observed Adverse Events: Major Depressive Disorder:** The most
 934 commonly observed adverse events associated with the use of paroxetine (incidence of 5% or
 935 greater and incidence for PAXIL at least twice that for placebo, derived from Table 2) were:
 936 Asthenia, sweating, nausea, decreased appetite, somnolence, dizziness, insomnia, tremor,
 937 nervousness, ejaculatory disturbance, and other male genital disorders.

938 **Obsessive Compulsive Disorder:** The most commonly observed adverse events
 939 associated with the use of paroxetine (incidence of 5% or greater and incidence for PAXIL at

940 least twice that of placebo, derived from Table 3) were: Nausea, dry mouth, decreased appetite,
941 constipation, dizziness, somnolence, tremor, sweating, impotence, and abnormal ejaculation.

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

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

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

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

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

969 **Major Depressive Disorder:** Table 2 enumerates adverse events that occurred at an
970 incidence of 1% or more among paroxetine-treated patients who participated in short-term
971 (6-week) placebo-controlled trials in which patients were dosed in a range of 20 mg to
972 50 mg/day. Reported adverse events were classified using a standard COSTART-based
973 Dictionary terminology.

974

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

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

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

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

- 983 c. Percentage corrected for gender.
- 984 d. Mostly “ejaculatory delay.”
- 985 e. Includes “anorgasmia,” “erectile difficulties,” “delayed ejaculation/orgasm,” and “sexual
- 986 dysfunction,” and “impotence.”
- 987 f. Includes mostly “difficulty with micturition” and “urinary hesitancy.”
- 988 g. Includes mostly “anorgasmia” and “difficulty reaching climax/orgasm.”

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

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

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

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

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

1002 a. Events reported by at least 2% of OCD, panic disorder, and social anxiety disorder in patients
1003 treated with PAXIL are included, except the following events which had an incidence on
1004 placebo \geq PAXIL: [OCD]: Abdominal pain, agitation, anxiety, back pain, cough increased,
1005 depression, headache, hyperkinesia, infection, paresthesia, pharyngitis, respiratory disorder,
1006 rhinitis, and sinusitis. [panic disorder]: Abnormal dreams, abnormal vision, chest pain, cough
1007 increased, depersonalization, depression, dysmenorrhea, dyspepsia, flu syndrome, headache,

1008 infection, myalgia, nervousness, palpitation, paresthesia, pharyngitis, rash, respiratory
1009 disorder, sinusitis, taste perversion, trauma, urination impaired, and vasodilation. [social
1010 anxiety disorder]: Abdominal pain, depression, headache, infection, respiratory disorder, and
1011 sinusitis.

1012 b. Percentage corrected for gender.

1013

1014 **Generalized Anxiety Disorder and Posttraumatic Stress Disorder:** Table 4
1015 enumerates adverse events that occurred at a frequency of 2% or more among GAD patients on
1016 PAXIL who participated in placebo-controlled trials of 8-weeks duration in which patients were
1017 dosed in a range of 10 mg/day to 50 mg/day or among PTSD patients on PAXIL who
1018 participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a
1019 range of 20 mg/day to 50 mg/day.

1020

1021 **Table 4. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled**
 1022 **Clinical Trials for Generalized Anxiety Disorder and Posttraumatic Stress Disorder^a**

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

- 1023 a. Events reported by at least 2% of GAD and PTSD in patients treated with PAXIL are
 1024 included, except the following events which had an incidence on placebo \geq PAXIL [GAD]:
 1025 Abdominal pain, back pain, trauma, dyspepsia, myalgia, and pharyngitis. [PTSD]: Back pain,
 1026 headache, anxiety, depression, nervousness, respiratory disorder, pharyngitis, and sinusitis.
 1027 b. Percentage corrected for gender.

1028
 1029 **Dose Dependency of Adverse Events:** A comparison of adverse event rates in a
 1030 fixed-dose study comparing 10, 20, 30, and 40 mg/day of PAXIL with placebo in the treatment
 1031 of major depressive disorder revealed a clear dose dependency for some of the more common
 1032 adverse events associated with use of PAXIL, as shown in Table 5:

1033
1034
1035

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

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

1036 a Rule for including adverse events in table: Incidence at least 5% for 1 of paroxetine groups
1037 and \geq twice the placebo incidence for at least 1 paroxetine group.

1038
1039 In a fixed-dose study comparing placebo and 20, 40, and 60 mg of PAXIL in the treatment of
1040 OCD, there was no clear relationship between adverse events and the dose of PAXIL to which
1041 patients were assigned. No new adverse events were observed in the group treated with 60 mg of
1042 PAXIL compared to any of the other treatment groups.

1043 In a fixed-dose study comparing placebo and 10, 20, and 40 mg of PAXIL in the treatment of
1044 panic disorder, there was no clear relationship between adverse events and the dose of PAXIL to
1045 which patients were assigned, except for asthenia, dry mouth, anxiety, libido decreased, tremor,
1046 and abnormal ejaculation. In flexible-dose studies, no new adverse events were observed in
1047 patients receiving 60 mg of PAXIL compared to any of the other treatment groups.

1048 In a fixed-dose study comparing placebo and 20, 40, and 60 mg of PAXIL in the treatment of
1049 social anxiety disorder, for most of the adverse events, there was no clear relationship between

1050 adverse events and the dose of PAXIL to which patients were assigned.

1051 In a fixed-dose study comparing placebo and 20 and 40 mg of PAXIL in the treatment of
1052 generalized anxiety disorder, for most of the adverse events, there was no clear relationship
1053 between adverse events and the dose of PAXIL to which patients were assigned, except for the
1054 following adverse events: Asthenia, constipation, and abnormal ejaculation.

1055 In a fixed-dose study comparing placebo and 20 and 40 mg of PAXIL in the treatment of
1056 posttraumatic stress disorder, for most of the adverse events, there was no clear relationship
1057 between adverse events and the dose of PAXIL to which patients were assigned, except for
1058 impotence and abnormal ejaculation.

1059 **Adaptation to Certain Adverse Events:** Over a 4- to 6-week period, there was evidence
1060 of adaptation to some adverse events with continued therapy (e.g., nausea and dizziness), but less
1061 to other effects (e.g., dry mouth, somnolence, and asthenia).

1062 **Male and Female Sexual Dysfunction With SSRIs:** Although changes in sexual desire,
1063 sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric
1064 disorder, they may also be a consequence of pharmacologic treatment. In particular, some
1065 evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward
1066 sexual experiences.

1067 Reliable estimates of the incidence and severity of untoward experiences involving sexual
1068 desire, performance, and satisfaction are difficult to obtain, however, in part because patients and
1069 physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of
1070 untoward sexual experience and performance cited in product labeling, are likely to
1071 underestimate their actual incidence.

1072 In placebo-controlled clinical trials involving more than 3,200 patients, the ranges for the
1073 reported incidence of sexual side effects in males and females with major depressive disorder,
1074 OCD, panic disorder, social anxiety disorder, GAD, and PTSD are displayed in Table 6.

1075

1076

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

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

1077

1078 There are no adequate and well-controlled studies examining sexual dysfunction with
1079 paroxetine treatment.

1080 Paroxetine treatment has been associated with several cases of priapism. In those cases with a
1081 known outcome, patients recovered without sequelae.

1082 While it is difficult to know the precise risk of sexual dysfunction associated with the use of

1083 SSRIs, physicians should routinely inquire about such possible side effects.

1084 **Weight and Vital Sign Changes:** Significant weight loss may be an undesirable result of
1085 treatment with PAXIL for some patients but, on average, patients in controlled trials had minimal
1086 (about 1 pound) weight loss versus smaller changes on placebo and active control. No significant
1087 changes in vital signs (systolic and diastolic blood pressure, pulse and temperature) were
1088 observed in patients treated with PAXIL in controlled clinical trials.

1089 **ECG Changes:** In an analysis of ECGs obtained in 682 patients treated with PAXIL and
1090 415 patients treated with placebo in controlled clinical trials, no clinically significant changes
1091 were seen in the ECGs of either group.

1092 **Liver Function Tests:** In placebo-controlled clinical trials, patients treated with PAXIL
1093 exhibited abnormal values on liver function tests at no greater rate than that seen in
1094 placebo-treated patients. In particular, the PAXIL-versus-placebo comparisons for alkaline
1095 phosphatase, SGOT, SGPT, and bilirubin revealed no differences in the percentage of patients
1096 with marked abnormalities.

1097 **Hallucinations:** In pooled clinical trials of immediate-release paroxetine hydrochloride,
1098 hallucinations were observed in 22 of 9089 patients receiving drug and 4 of 3187 patients
1099 receiving placebo.

1100 **Other Events Observed During the Premarketing Evaluation of PAXIL:** During its
1101 premarketing assessment in major depressive disorder, multiple doses of PAXIL were
1102 administered to 6,145 patients in phase 2 and 3 studies. The conditions and duration of exposure
1103 to PAXIL varied greatly and included (in overlapping categories) open and double-blind studies,
1104 uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose, and titration
1105 studies. During premarketing clinical trials in OCD, panic disorder, social anxiety disorder,
1106 generalized anxiety disorder, and posttraumatic stress disorder, 542, 469, 522, 735, and 676
1107 patients, respectively, received multiple doses of PAXIL. Untoward events associated with this
1108 exposure were recorded by clinical investigators using terminology of their own choosing.
1109 Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals
1110 experiencing adverse events without first grouping similar types of untoward events into a
1111 smaller number of standardized event categories.

1112 In the tabulations that follow, reported adverse events were classified using a standard
1113 COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the
1114 proportion of the 9,089 patients exposed to multiple doses of PAXIL who experienced an event
1115 of the type cited on at least 1 occasion while receiving PAXIL. All reported events are included
1116 except those already listed in Tables 2 to 5, those reported in terms so general as to be
1117 uninformative and those events where a drug cause was remote. It is important to emphasize that
1118 although the events reported occurred during treatment with paroxetine, they were not
1119 necessarily caused by it.

1120 Events are further categorized by body system and listed in order of decreasing frequency
1121 according to the following definitions: Frequent adverse events are those occurring on 1 or more
1122 occasions in at least 1/100 patients (only those not already listed in the tabulated results from

1123 placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in
1124 1/100 to 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients. Events
1125 of major clinical importance are also described in the PRECAUTIONS section.

1126 **Body as a Whole:** *Infrequent:* Allergic reaction, chills, face edema, malaise, neck pain;
1127 *rare:* Adrenergic syndrome, cellulitis, moniliasis, neck rigidity, pelvic pain, peritonitis, sepsis,
1128 ulcer.

1129 **Cardiovascular System:** *Frequent:* Hypertension, tachycardia; *infrequent:* Bradycardia,
1130 hematoma, hypotension, migraine, postural hypotension, syncope; *rare:* Angina pectoris,
1131 arrhythmia nodal, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular
1132 accident, congestive heart failure, heart block, low cardiac output, myocardial infarct, myocardial
1133 ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis,
1134 thrombosis, varicose vein, vascular headache, ventricular extrasystoles.

1135 **Digestive System:** *Infrequent:* Bruxism, colitis, dysphagia, eructation, gastritis,
1136 gastroenteritis, gingivitis, glossitis, increased salivation, liver function tests abnormal, rectal
1137 hemorrhage, ulcerative stomatitis; *rare:* Aphthous stomatitis, bloody diarrhea, bulimia,
1138 cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal
1139 incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, intestinal obstruction,
1140 jaundice, melena, mouth ulceration, peptic ulcer, salivary gland enlargement, sialadenitis,
1141 stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries.

1142 **Endocrine System:** *Rare:* Diabetes mellitus, goiter, hyperthyroidism, hypothyroidism,
1143 thyroiditis.

1144 **Hemic and Lymphatic Systems:** *Infrequent:* Anemia, leukopenia, lymphadenopathy,
1145 purpura; *rare:* Abnormal erythrocytes, basophilia, bleeding time increased, eosinophilia,
1146 hypochromic anemia, iron deficiency anemia, leukocytosis, lymphedema, abnormal
1147 lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia,
1148 thrombocythemia, thrombocytopenia.

1149 **Metabolic and Nutritional:** *Frequent:* Weight gain; *infrequent:* Edema, peripheral edema,
1150 SGOT increased, SGPT increased, thirst, weight loss; *rare:* Alkaline phosphatase increased,
1151 bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, gamma
1152 globulins increased, gout, hypercalcemia, hypercholesteremia, hyperglycemia, hyperkalemia,
1153 hyperphosphatemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, ketosis, lactic
1154 dehydrogenase increased, non-protein nitrogen (NPN) increased.

1155 **Musculoskeletal System:** *Frequent:* Arthralgia; *infrequent:* Arthritis, arthrosis; *rare:*
1156 Bursitis, myositis, osteoporosis, generalized spasm, tenosynovitis, tetany.

1157 **Nervous System:** *Frequent:* Emotional lability, vertigo; *infrequent:* Abnormal thinking,
1158 alcohol abuse, ataxia, dystonia, dyskinesia, euphoria, hallucinations, hostility, hypertonia,
1159 hypesthesia, hypokinesia, incoordination, lack of emotion, libido increased, manic reaction,
1160 neurosis, paralysis, paranoid reaction; *rare:* Abnormal gait, akinesia, antisocial reaction, aphasia,
1161 choreoathetosis, circumoral paresthesias, convulsion, delirium, delusions, diplopia, drug
1162 dependence, dysarthria, extrapyramidal syndrome, fasciculations, grand mal convulsion,

1163 hyperalgesia, hysteria, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy,
1164 nystagmus, peripheral neuritis, psychotic depression, psychosis, reflexes decreased, reflexes
1165 increased, stupor, torticollis, trismus, withdrawal syndrome.

1166 **Respiratory System:** *Infrequent:* Asthma, bronchitis, dyspnea, epistaxis, hyperventilation,
1167 pneumonia, respiratory flu; *rare:* Emphysema, hemoptysis, hiccups, lung fibrosis, pulmonary
1168 edema, sputum increased, stridor, voice alteration.

1169 **Skin and Appendages:** *Frequent:* Pruritus; *infrequent:* Acne, alopecia, contact dermatitis,
1170 dry skin, ecchymosis, eczema, herpes simplex, photosensitivity, urticaria; *rare:* Angioedema,
1171 erythema nodosum, erythema multiforme, exfoliative dermatitis, fungal dermatitis, furunculosis;
1172 herpes zoster, hirsutism, maculopapular rash, seborrhea, skin discoloration, skin hypertrophy,
1173 skin ulcer, sweating decreased, vesiculobullous rash.

1174 **Special Senses:** *Frequent:* Tinnitus; *infrequent:* Abnormality of accommodation,
1175 conjunctivitis, ear pain, eye pain, keratoconjunctivitis, mydriasis, otitis media; *rare:* Amblyopia,
1176 anisocoria, blepharitis, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, eye
1177 hemorrhage, glaucoma, hyperacusis, night blindness, otitis externa, parosmia, photophobia,
1178 ptosis, retinal hemorrhage, taste loss, visual field defect.

1179 **Urogenital System:** *Infrequent:* Amenorrhea, breast pain, cystitis, dysuria, hematuria,
1180 menorrhagia, nocturia, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency,
1181 vaginitis; *rare:* Abortion, breast atrophy, breast enlargement, endometrial disorder, epididymitis,
1182 female lactation, fibrocystic breast, kidney calculus, kidney pain, leukorrhea, mastitis,
1183 metrorrhagia, nephritis, oliguria, salpingitis, urethritis, urinary casts, uterine spasm, urolith,
1184 vaginal hemorrhage, vaginal moniliasis.

1185 **Postmarketing Reports:** Voluntary reports of adverse events in patients taking PAXIL that
1186 have been received since market introduction and not listed above that may have no causal
1187 relationship with the drug include acute pancreatitis, elevated liver function tests (the most
1188 severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated
1189 with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism,
1190 syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and
1191 galactorrhea; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel
1192 rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use
1193 of pimozide; tremor and trismus; status epilepticus, acute renal failure, pulmonary hypertension,
1194 allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, restless legs
1195 syndrome (RLS), ventricular fibrillation, ventricular tachycardia (including torsade de pointes),
1196 thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including
1197 aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic
1198 syndromes (such as Henoch-Schönlein purpura). There has been a case report of an elevated
1199 phenytoin level after 4 weeks of PAXIL and phenytoin coadministration. There has been a case
1200 report of severe hypotension when PAXIL was added to chronic metoprolol treatment.

1201 **DRUG ABUSE AND DEPENDENCE**

1202 **Controlled Substance Class:** PAXIL is not a controlled substance.

1203 **Physical and Psychologic Dependence:** PAXIL has not been systematically studied in
1204 animals or humans for its potential for abuse, tolerance or physical dependence. While the
1205 clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were
1206 not systematic and it is not possible to predict on the basis of this limited experience the extent to
1207 which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently,
1208 patients should be evaluated carefully for history of drug abuse, and such patients should be
1209 observed closely for signs of misuse or abuse of PAXIL (e.g., development of tolerance,
1210 incrementations of dose, drug-seeking behavior).

1211 **OVERDOSAGE**

1212 **Human Experience:** Since the introduction of PAXIL in the United States, 342 spontaneous
1213 cases of deliberate or accidental overdosage during paroxetine treatment have been reported
1214 worldwide (circa 1999). These include overdoses with paroxetine alone and in combination with
1215 other substances. Of these, 48 cases were fatal and of the fatalities, 17 appeared to involve
1216 paroxetine alone. Eight fatal cases that documented the amount of paroxetine ingested were
1217 generally confounded by the ingestion of other drugs or alcohol or the presence of significant
1218 comorbid conditions. Of 145 non-fatal cases with known outcome, most recovered without
1219 sequelae. The largest known ingestion involved 2,000 mg of paroxetine (33 times the maximum
1220 recommended daily dose) in a patient who recovered.

1221 Commonly reported adverse events associated with paroxetine overdosage include
1222 somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other
1223 notable signs and symptoms observed with overdoses involving paroxetine (alone or with other
1224 substances) include mydriasis, convulsions (including status epilepticus), ventricular
1225 dysrhythmias (including torsade de pointes), hypertension, aggressive reactions, syncope,
1226 hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction
1227 (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin
1228 syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

1229 **Overdosage Management:** No specific antidotes for paroxetine are known. Treatment
1230 should consist of those general measures employed in the management of overdosage with any
1231 drugs effective in the treatment of major depressive disorder.

1232 Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital
1233 signs. General supportive and symptomatic measures are also recommended. Induction of emesis
1234 is not recommended. Due to the large volume of distribution of this drug, forced diuresis,
1235 dialysis, hemoperfusion, or exchange perfusion are unlikely to be of benefit.

1236 A specific caution involves patients who are taking or have recently taken paroxetine who
1237 might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the
1238 parent tricyclic and/or an active metabolite may increase the possibility of clinically significant
1239 sequelae and extend the time needed for close medical observation (see PRECAUTIONS: *Drugs*

1240 *Metabolized by Cytochrome CYP2D6).*

1241 In managing overdose, consider the possibility of multiple drug involvement. The physician
1242 should consider contacting a poison control center for additional information on the treatment of
1243 any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians'*
1244 *Desk Reference* (PDR).

1245 **DOSAGE AND ADMINISTRATION**

1246 **Major Depressive Disorder: Usual Initial Dosage:** PAXIL should be administered as a
1247 single daily dose with or without food, usually in the morning. The recommended initial dose is
1248 20 mg/day. Patients were dosed in a range of 20 to 50 mg/day in the clinical trials demonstrating
1249 the effectiveness of PAXIL in the treatment of major depressive disorder. As with all drugs
1250 effective in the treatment of major depressive disorder, the full effect may be delayed. Some
1251 patients not responding to a 20-mg dose may benefit from dose increases, in 10-mg/day
1252 increments, up to a maximum of 50 mg/day. Dose changes should occur at intervals of at least
1253 1 week.

1254 **Maintenance Therapy:** There is no body of evidence available to answer the question of
1255 how long the patient treated with PAXIL should remain on it. It is generally agreed that acute
1256 episodes of major depressive disorder require several months or longer of sustained
1257 pharmacologic therapy. Whether the dose needed to induce remission is identical to the dose
1258 needed to maintain and/or sustain euthymia is unknown.

1259 Systematic evaluation of the efficacy of PAXIL has shown that efficacy is maintained for
1260 periods of up to 1 year with doses that averaged about 30 mg.

1261 **Obsessive Compulsive Disorder: Usual Initial Dosage:** PAXIL should be administered
1262 as a single daily dose with or without food, usually in the morning. The recommended dose of
1263 PAXIL in the treatment of OCD is 40 mg daily. Patients should be started on 20 mg/day and the
1264 dose can be increased in 10-mg/day increments. Dose changes should occur at intervals of at
1265 least 1 week. Patients were dosed in a range of 20 to 60 mg/day in the clinical trials
1266 demonstrating the effectiveness of PAXIL in the treatment of OCD. The maximum dosage
1267 should not exceed 60 mg/day.

1268 **Maintenance Therapy:** Long-term maintenance of efficacy was demonstrated in a 6-month
1269 relapse prevention trial. In this trial, patients with OCD assigned to paroxetine demonstrated a
1270 lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY:
1271 Clinical Trials). OCD is a chronic condition, and it is reasonable to consider continuation for a
1272 responding patient. Dosage adjustments should be made to maintain the patient on the lowest
1273 effective dosage, and patients should be periodically reassessed to determine the need for
1274 continued treatment.

1275 **Panic Disorder: Usual Initial Dosage:** PAXIL should be administered as a single daily dose
1276 with or without food, usually in the morning. The target dose of PAXIL in the treatment of panic
1277 disorder is 40 mg/day. Patients should be started on 10 mg/day. Dose changes should occur in
1278 10-mg/day increments and at intervals of at least 1 week. Patients were dosed in a range of 10 to

1279 60 mg/day in the clinical trials demonstrating the effectiveness of PAXIL. The maximum dosage
1280 should not exceed 60 mg/day.

1281 **Maintenance Therapy:** Long-term maintenance of efficacy was demonstrated in a 3-month
1282 relapse prevention trial. In this trial, patients with panic disorder assigned to paroxetine
1283 demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL
1284 PHARMACOLOGY: Clinical Trials). Panic disorder is a chronic condition, and it is reasonable
1285 to consider continuation for a responding patient. Dosage adjustments should be made to
1286 maintain the patient on the lowest effective dosage, and patients should be periodically
1287 reassessed to determine the need for continued treatment.

1288 **Social Anxiety Disorder: Usual Initial Dosage:** PAXIL should be administered as a single
1289 daily dose with or without food, usually in the morning. The recommended and initial dosage is
1290 20 mg/day. In clinical trials the effectiveness of PAXIL was demonstrated in patients dosed in a
1291 range of 20 to 60 mg/day. While the safety of PAXIL has been evaluated in patients with social
1292 anxiety disorder at doses up to 60 mg/day, available information does not suggest any additional
1293 benefit for doses above 20 mg/day (see CLINICAL PHARMACOLOGY: Clinical Trials).

1294 **Maintenance Therapy:** There is no body of evidence available to answer the question of
1295 how long the patient treated with PAXIL should remain on it. Although the efficacy of PAXIL
1296 beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials, social anxiety
1297 disorder is recognized as a chronic condition, and it is reasonable to consider continuation of
1298 treatment for a responding patient. Dosage adjustments should be made to maintain the patient
1299 on the lowest effective dosage, and patients should be periodically reassessed to determine the
1300 need for continued treatment.

1301 **Generalized Anxiety Disorder: Usual Initial Dosage:** PAXIL should be administered as a
1302 single daily dose with or without food, usually in the morning. In clinical trials the effectiveness
1303 of PAXIL was demonstrated in patients dosed in a range of 20 to 50 mg/day. The recommended
1304 starting dosage and the established effective dosage is 20 mg/day. There is not sufficient
1305 evidence to suggest a greater benefit to doses higher than 20 mg/day. Dose changes should occur
1306 in 10 mg/day increments and at intervals of at least 1 week.

1307 **Maintenance Therapy:** Systematic evaluation of continuing PAXIL for periods of up to
1308 24 weeks in patients with Generalized Anxiety Disorder who had responded while taking PAXIL
1309 during an 8-week acute treatment phase has demonstrated a benefit of such maintenance (see
1310 CLINICAL PHARMACOLOGY: Clinical Trials). Nevertheless, patients should be periodically
1311 reassessed to determine the need for maintenance treatment.

1312 **Posttraumatic Stress Disorder: Usual Initial Dosage:** PAXIL should be administered as
1313 a single daily dose with or without food, usually in the morning. The recommended starting
1314 dosage and the established effective dosage is 20 mg/day. In 1 clinical trial, the effectiveness of
1315 PAXIL was demonstrated in patients dosed in a range of 20 to 50 mg/day. However, in a fixed
1316 dose study, there was not sufficient evidence to suggest a greater benefit for a dose of 40 mg/day
1317 compared to 20 mg/day. Dose changes, if indicated, should occur in 10 mg/day increments and at
1318 intervals of at least 1 week.

1319 **Maintenance Therapy:** There is no body of evidence available to answer the question of
1320 how long the patient treated with PAXIL should remain on it. Although the efficacy of PAXIL
1321 beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials, PTSD is
1322 recognized as a chronic condition, and it is reasonable to consider continuation of treatment for a
1323 responding patient. Dosage adjustments should be made to maintain the patient on the lowest
1324 effective dosage, and patients should be periodically reassessed to determine the need for
1325 continued treatment.

1326 **Special Populations: Treatment of Pregnant Women During the Third Trimester:**

1327 Neonates exposed to PAXIL and other SSRIs or SNRIs, late in the third trimester have
1328 developed complications requiring prolonged hospitalization, respiratory support, and tube
1329 feeding (see WARNINGS: Usage in Pregnancy). When treating pregnant women with paroxetine
1330 during the third trimester, the physician should carefully consider the potential risks and benefits
1331 of treatment. The physician may consider tapering paroxetine in the third trimester.

1332 **Dosage for Elderly or Debilitated Patients, and Patients With Severe Renal or**
1333 **Hepatic Impairment:** The recommended initial dose is 10 mg/day for elderly patients,
1334 debilitated patients, and/or patients with severe renal or hepatic impairment. Increases may be
1335 made if indicated. Dosage should not exceed 40 mg/day.

1336 **Switching Patients to or From a Monoamine Oxidase Inhibitor:** At least 14 days
1337 should elapse between discontinuation of an MAOI and initiation of therapy with PAXIL.
1338 Similarly, at least 14 days should be allowed after stopping PAXIL before starting an MAOI.

1339 **Discontinuation of Treatment With PAXIL:** Symptoms associated with discontinuation of
1340 PAXIL have been reported (see PRECAUTIONS: *Discontinuation of Treatment With*
1341 *PAXIL*). Patients should be monitored for these symptoms when discontinuing treatment,
1342 regardless of the indication for which PAXIL is being prescribed. A gradual reduction in the
1343 dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms
1344 occur following a decrease in the dose or upon discontinuation of treatment, then resuming the
1345 previously prescribed dose may be considered. Subsequently, the physician may continue
1346 decreasing the dose but at a more gradual rate.

1347 **NOTE: SHAKE SUSPENSION WELL BEFORE USING.**

1348 **HOW SUPPLIED**

1349 **Tablets:** Film-coated, modified-oval as follows:

1350 10-mg yellow, scored tablets engraved on the front with PAXIL and on the back with 10.

1351 NDC 0029-3210-13 Bottles of 30

1352 20-mg pink, scored tablets engraved on the front with PAXIL and on the back with 20.

1353 NDC 0029-3211-13 Bottles of 30

1354 NDC 0029-3211-59 Bottles of 90

1355 NDC 0029-3211-21 SUP 100s (intended for institutional use only)

1356 30-mg blue tablets engraved on the front with PAXIL and on the back with 30.

1357 NDC 0029-3212-13 Bottles of 30

1358 40-mg green tablets engraved on the front with PAXIL and on the back with 40.
1359 NDC 0029-3213-13 Bottles of 30
1360 Store tablets between 15° and 30°C (59° and 86°F).
1361 **Oral Suspension:** Orange-colored, orange-flavored, 10 mg/5 mL, in 250 mL white bottles.
1362 NDC 0029-3215-48
1363 Store suspension at or below 25°C (77°F).
1364 PAXIL is a registered trademark of GlaxoSmithKline.
1365

1366 Medication Guide

1368 Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal 1369 Thoughts or Actions

1370 PAXIL® (PAX-il) (paroxetine hydrochloride) Tablets and Oral Suspension

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1372 Read the Medication Guide that comes with your or your family member's antidepressant
1373 medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with
1374 antidepressant medicines. **Talk to your, or your family member's, healthcare provider**
1375 **about:**

- 1376 • All risks and benefits of treatment with antidepressant medicines
- 1377 • All treatment choices for depression or other serious mental illness

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1379 **What is the most important information I should know about antidepressant medicines,**
1380 **depression and other serious mental illnesses, and suicidal thoughts or action?**

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- 1382 **1. Antidepressant medicines may increase suicidal thoughts or actions in some children,**
1383 **teenagers, and young adults within the first few months of treatment.**
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1385 **2. Depression and other serious mental illnesses are the most important causes of suicidal**
1386 **thoughts and actions. Some people may have a particularly high risk of having suicidal**
1387 **thoughts or actions.** These include people who have (or have a family history of) bipolar
1388 illness (also called manic-depressive illness) or suicidal thoughts or actions.
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1390 **3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a**
1391 **family member?**
 - 1392 • Pay close attention to any changes, especially sudden changes, in mood, behaviors,
1393 thoughts, or feelings. This is very important when an antidepressant medicine is started or
1394 when the dose is changed.
 - 1395 • Call the healthcare provider right away to report new or sudden changes in mood,
1396 behavior, thoughts, or feelings.
 - 1397 • Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare
1398 provider between visits as needed, especially if you have concerns about symptoms.

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1400 **Call a healthcare provider right away if you or your family member has any of the**
1401 **following symptoms, especially if they are new, worse, or worry you:**

- 1402 • Thoughts about suicide or dying
- 1403 • Attempts to commit suicide
- 1404 • New or worse depression
- 1405 • New or worse anxiety
- 1406 • Feeling very agitated or restless
- 1407 • Panic attacks
- 1408 • Trouble sleeping (insomnia)
- 1409 • New or worse irritability
- 1410 • Acting aggressive, being angry, or violent
- 1411 • Acting on dangerous impulses
- 1412 • An extreme increase in activity and talking (mania)
- 1413 • Other unusual changes in behavior or mood

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1415 **What else do I need to know about antidepressant medicines?**

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- 1417 • **Never stop an antidepressant medicine without first talking to a healthcare**
1418 **provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
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- 1420 • **Antidepressants are medicines used to treat depression and other illnesses.** It is
1421 important to discuss all the risks of treating depression and also the risks of not treating it.
1422 Patients and their families or other caregivers should discuss all treatment choices with
1423 the healthcare provider, not just the use of antidepressants.
- 1424
- 1425 • **Antidepressant medicines have other side effects.** Call your doctor for medical advice
1426 about side effects. You may report side effects to FDA at 1-800-FDA-1088.
- 1427
- 1428 • **Antidepressant medicines can interact with other medicines.** Know all of the
1429 medicines that you or your family member takes. Keep a list of all medicines to show the
1430 healthcare provider. Do not start new medicines without first checking with your
1431 healthcare provider.
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- 1433 • **Not all antidepressant medicines prescribed for children are FDA approved for use**
1434 **in children.** Talk to your child's healthcare provider for more information.

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1436 This Medication Guide has been approved by the U.S. Food and Drug Administration for all
1437 antidepressants.

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