

## PRESCRIBING INFORMATION

# PAXIL<sup>®</sup>

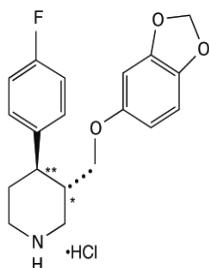
(paroxetine hydrochloride)  
Tablets and Oral Suspension

### Suicidality and Antidepressant Drugs

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

### DESCRIPTION

PAXIL (paroxetine hydrochloride) is an orally administered psychotropic drug. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-*trans*-4*R*-(4'-fluorophenyl)-3*S*-[(3',4'-methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate and has the empirical formula of C<sub>19</sub>H<sub>20</sub>FNO<sub>3</sub>•HCl•1/2H<sub>2</sub>O. The molecular weight is 374.8 (329.4 as free base). The structural formula of paroxetine hydrochloride is:



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

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

34 the following: D&C Red No. 30 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,  $\alpha_1$ -,  $\alpha_2$ -, beta-adrenergic-, dopamine  
52 ( $D_2$ )-, 5-HT<sub>1</sub>-, 5-HT<sub>2</sub>-, and histamine ( $H_1$ )-receptors; antagonism of muscarinic, histaminergic,  
53 and  $\alpha_1$ -adrenergic receptors has been associated with various anticholinergic, sedative, and  
54 cardiovascular effects for other psychotropic drugs.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## 127 **Clinical Trials**

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

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

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

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

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

157

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

158

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

223 Study 2 was a flexible-dose study comparing paroxetine (20 mg to 50 mg daily) and placebo.

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

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

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

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

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

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

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

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

## 269 **INDICATIONS AND USAGE**

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

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

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

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

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

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

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

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

302 **Panic Disorder:** PAXIL is indicated for the treatment of panic disorder, with or without



303 agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of  
304 unexpected panic attacks and associated concern about having additional attacks, worry about  
305 the implications or consequences of the attacks, and/or a significant change in behavior related to  
306 the attacks.

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

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

318 Long-term maintenance of efficacy was demonstrated in a 3-month relapse prevention trial. In  
319 this trial, patients with panic disorder assigned to paroxetine demonstrated a lower relapse rate  
320 compared to patients on placebo (see CLINICAL PHARMACOLOGY: Clinical Trials).

321 Nevertheless, the physician who prescribes PAXIL for extended periods should periodically  
322 re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND  
323 ADMINISTRATION).

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

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

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

342 **Generalized Anxiety Disorder:** PAXIL is indicated for the treatment of Generalized Anxiety

343 Disorder (GAD), as defined in DSM-IV. Anxiety or tension associated with the stress of  
344 everyday life usually does not require treatment with an anxiolytic.

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

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

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

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

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

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

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

383 **CONTRAINDICATIONS**

384 The use of MAOIs intended to treat depression with, or within 14 days of treatment with,  
385 PAXIL is contraindicated (see WARNINGS).

386 Do not start PAXIL in a patient who is being treated with a reversible MAOI such as linezolid  
387 or methylene blue because of an increased risk of serotonin syndrome or neuroleptic malignant  
388 syndrome (NMS)-like reactions (see WARNINGS).

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

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

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

394 **WARNINGS**

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

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

420

421 **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

422

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

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

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

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

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

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

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

453 **emergence of suicidality, and to report such symptoms immediately to healthcare**  
454 **providers. Such monitoring should include daily observation by families and caregivers.**

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

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

466 **Potential for Interaction With Monoamine Oxidase Inhibitors:** In patients receiving  
467 another serotonin reuptake inhibitor drug in combination with monoamine oxidase inhibitors  
468 (MAOIs), including reversible MAOIs such as linezolid and methylene blue, there have been  
469 reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus,  
470 autonomic instability with possible rapid fluctuations of vital signs, and mental status changes  
471 that include extreme agitation progressing to delirium and coma. These reactions have also been  
472 reported in patients who have recently discontinued that drug and have been started on an MAOI.  
473 Some cases presented with features resembling serotonin syndrome or NMS-like reactions (see  
474 CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).

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

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

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

493 **during treatment initiation and dose increases.**

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

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

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

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

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

- 511 • A study based on Swedish national registry data demonstrated that infants exposed to  
512 paroxetine during pregnancy (n = 815) had an increased risk of cardiovascular  
513 malformations (2% risk in paroxetine-exposed infants) compared to the entire registry  
514 population (1% risk), for an odds ratio (OR) of 1.8 (95% confidence interval 1.1 to 2.8). No  
515 increase in the risk of overall congenital malformations was seen in the paroxetine-exposed  
516 infants. The cardiac malformations in the paroxetine-exposed infants were primarily  
517 ventricular septal defects (VSDs) and atrial septal defects (ASDs). Septal defects range in  
518 severity from those that resolve spontaneously to those which require surgery.
- 519 • A separate retrospective cohort study from the United States (United Healthcare data)  
520 evaluated 5,956 infants of mothers dispensed antidepressants during the first trimester  
521 (n = 815 for paroxetine). This study showed a trend towards an increased risk for  
522 cardiovascular malformations for paroxetine (risk of 1.5%) compared to other  
523 antidepressants (risk of 1%), for an OR of 1.5 (95% confidence interval 0.8 to 2.9). Of the  
524 12 paroxetine-exposed infants with cardiovascular malformations, 9 had VSDs. This study  
525 also suggested an increased risk of overall major congenital malformations including  
526 cardiovascular defects for paroxetine (4% risk) compared to other (2% risk) antidepressants  
527 (OR 1.8; 95% confidence interval 1.2 to 2.8).
- 528 • Two large case-control studies using separate databases, each with >9,000 birth defect  
529 cases and >4,000 controls, found that maternal use of paroxetine during the first trimester  
530 of pregnancy was associated with a 2- to 3-fold increased risk of right ventricular outflow  
531 tract obstructions. In one study the odds ratio was 2.5 (95% confidence interval, 1.0 to 6.0,  
532 7 exposed infants) and in the other study the odds ratio was 3.3 (95% confidence interval,

533 1.3 to 8.8, 6 exposed infants).

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

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

553 **Animal Findings:** Reproduction studies were performed at doses up to 50 mg/kg/day in rats  
554 and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately  
555 8 (rat) and 2 (rabbit) times the maximum recommended human dose (MRHD) on an mg/m<sup>2</sup>  
556 basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was  
557 an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last  
558 trimester of gestation and continued throughout lactation. This effect occurred at a dose of  
559 1 mg/kg/day or approximately one-sixth of the MRHD on an mg/m<sup>2</sup> basis. The no-effect dose for  
560 rat pup mortality was not determined. The cause of these deaths is not known.

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

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

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

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

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

## 589 **PRECAUTIONS**

590 **General: Activation of Mania/Hypomania:** During premarketing testing, hypomania or  
591 mania occurred in approximately 1.0% of unipolar patients treated with PAXIL compared to  
592 1.1% of active-control and 0.3% of placebo-treated unipolar patients. In a subset of patients  
593 classified as bipolar, the rate of manic episodes was 2.2% for PAXIL and 11.6% for the  
594 combined active-control groups. As with all drugs effective in the treatment of major depressive  
595 disorder, PAXIL should be used cautiously in patients with a history of mania.

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

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

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

610 During marketing of PAXIL and other SSRIs and SNRIs, there have been spontaneous reports  
611 of adverse events occurring upon the discontinuation of these drugs (particularly when abrupt),



612 including the following: Dysphoric mood, irritability, agitation, dizziness, sensory disturbances  
613 (e.g., paresthesias such as electric shock sensations and tinnitus), anxiety, confusion, headache,  
614 lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-  
615 limiting, there have been reports of serious discontinuation symptoms.

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

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

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

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

636 **Hyponatremia:** Hyponatremia may occur as a result of treatment with SSRIs and SNRIs,  
637 including PAXIL. In many cases, this hyponatremia appears to be the result of the syndrome of  
638 inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than  
639 110 mmol/L have been reported. Elderly patients may be at greater risk of developing  
640 hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise  
641 volume depleted may be at greater risk (see PRECAUTIONS: Geriatric Use). Discontinuation of  
642 PAXIL should be considered in patients with symptomatic hyponatremia and appropriate  
643 medical intervention should be instituted.

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

648 **Abnormal Bleeding:** SSRIs and SNRIs, including paroxetine, may increase the risk of  
649 bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and  
650 other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control  
651 and cohort design) have demonstrated an association between use of drugs that interfere with

652 serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to  
653 SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to  
654 life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated  
655 with the concomitant use of paroxetine and NSAIDs, aspirin, or other drugs that affect  
656 coagulation.

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

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

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

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

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

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

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

686 Prescribers or other health professionals should inform patients, their families, and their  
687 caregivers about the benefits and risks associated with treatment with PAXIL and should counsel  
688 them in its appropriate use. A patient Medication Guide is available for PAXIL. The prescriber  
689 or health professional should instruct patients, their families, and their caregivers to read the  
690 Medication Guide and should assist them in understanding its contents. Patients should be given  
691 the opportunity to discuss the contents of the Medication Guide and to obtain answers to any

692 questions they may have. The complete text of the Medication Guide is reprinted at the end of  
693 this document.

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

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

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

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

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

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

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

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

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

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

730 **Drug Interactions: Tryptophan:** As with other serotonin reuptake inhibitors, an interaction  
731 between paroxetine and tryptophan may occur when they are coadministered. Adverse

732 experiences, consisting primarily of headache, nausea, sweating, and dizziness, have been  
733 reported when tryptophan was administered to patients taking PAXIL. Consequently,  
734 concomitant use of PAXIL with tryptophan is not recommended (see WARNINGS: Serotonin  
735 Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions).

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

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

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

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

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

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

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

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

766 **Cimetidine:** Cimetidine inhibits many cytochrome P<sub>450</sub> (oxidative) enzymes. In a study  
767 where PAXIL (30 mg once daily) was dosed orally for 4 weeks, steady-state plasma  
768 concentrations of paroxetine were increased by approximately 50% during coadministration with  
769 oral cimetidine (300 mg three times daily) for the final week. Therefore, when these drugs are  
770 administered concurrently, dosage adjustment of PAXIL after the 20-mg starting dose should be  
771 guided by clinical effect. The effect of paroxetine on cimetidine's pharmacokinetics was not

772 studied.

773 **Phenobarbital:** Phenobarbital induces many cytochrome P<sub>450</sub> (oxidative) enzymes. When a  
774 single oral 30-mg dose of PAXIL was administered at phenobarbital steady state (100 mg once  
775 daily for 14 days), paroxetine AUC and T<sub>1/2</sub> were reduced (by an average of 25% and 38%,  
776 respectively) compared to paroxetine administered alone. The effect of paroxetine on  
777 phenobarbital pharmacokinetics was not studied. Since PAXIL exhibits nonlinear  
778 pharmacokinetics, the results of this study may not address the case where the 2 drugs are both  
779 being chronically dosed. No initial dosage adjustment of PAXIL is considered necessary when  
780 coadministered with phenobarbital; any subsequent adjustment should be guided by clinical  
781 effect.

782 **Phenytoin:** When a single oral 30-mg dose of PAXIL was administered at phenytoin steady  
783 state (300 mg once daily for 14 days), paroxetine AUC and T<sub>1/2</sub> were reduced (by an average of  
784 50% and 35%, respectively) compared to PAXIL administered alone. In a separate study, when a  
785 single oral 300-mg dose of phenytoin was administered at paroxetine steady state (30 mg once  
786 daily for 14 days), phenytoin AUC was slightly reduced (12% on average) compared to  
787 phenytoin administered alone. Since both drugs exhibit nonlinear pharmacokinetics, the above  
788 studies may not address the case where the 2 drugs are both being chronically dosed. No initial  
789 dosage adjustments are considered necessary when these drugs are coadministered; any  
790 subsequent adjustments should be guided by clinical effect (see ADVERSE REACTIONS:  
791 Postmarketing Reports).

792 **Drugs Metabolized by CYP2D6:** Many drugs, including most drugs effective in the  
793 treatment of major depressive disorder (paroxetine, other SSRIs and many tricyclics), are  
794 metabolized by the cytochrome P<sub>450</sub> isozyme CYP2D6. Like other agents that are metabolized by  
795 CYP2D6, paroxetine may significantly inhibit the activity of this isozyme. In most patients  
796 (>90%), this CYP2D6 isozyme is saturated early during dosing with PAXIL. In 1 study, daily  
797 dosing of PAXIL (20 mg once daily) under steady-state conditions increased single dose  
798 desipramine (100 mg) C<sub>max</sub>, AUC, and T<sub>1/2</sub> by an average of approximately 2-, 5-, and 3-fold,  
799 respectively. Concomitant use of paroxetine with risperidone, a CYP2D6 substrate has also been  
800 evaluated. In 1 study, daily dosing of paroxetine 20 mg in patients stabilized on risperidone (4 to  
801 8 mg/day) increased mean plasma concentrations of risperidone approximately 4-fold, decreased  
802 9-hydroxyrisperidone concentrations approximately 10%, and increased concentrations of the  
803 active moiety (the sum of risperidone plus 9-hydroxyrisperidone) approximately 1.4-fold. The  
804 effect of paroxetine on the pharmacokinetics of atomoxetine has been evaluated when both drugs  
805 were at steady state. In healthy volunteers who were extensive metabolizers of CYP2D6,  
806 paroxetine 20 mg daily was given in combination with 20 mg atomoxetine every 12 hours. This  
807 resulted in increases in steady state atomoxetine AUC values that were 6- to 8-fold greater and in  
808 atomoxetine C<sub>max</sub> values that were 3- to 4-fold greater than when atomoxetine was given alone.  
809 Dosage adjustment of atomoxetine may be necessary and it is recommended that atomoxetine be  
810 initiated at a reduced dose when it is given with paroxetine.

811 Concomitant use of PAXIL with other drugs metabolized by cytochrome CYP2D6 has not

812 been formally studied but may require lower doses than usually prescribed for either PAXIL or  
813 the other drug.

814 Therefore, coadministration of PAXIL with other drugs that are metabolized by this isozyme,  
815 including certain drugs effective in the treatment of major depressive disorder (e.g., nortriptyline,  
816 amitriptyline, imipramine, desipramine, and fluoxetine), phenothiazines, risperidone, and Type  
817 1C antiarrhythmics (e.g., propafenone, flecainide, and encainide), or that inhibit this enzyme  
818 (e.g., quinidine), should be approached with caution.

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

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

825 At steady state, when the CYP2D6 pathway is essentially saturated, paroxetine clearance is  
826 governed by alternative P<sub>450</sub> isozymes that, unlike CYP2D6, show no evidence of saturation (see  
827 PRECAUTIONS: *Tricyclic Antidepressants [TCAs]*).

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

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

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

848 **Drugs That Interfere With Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin):**  
849 Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of  
850 the case-control and cohort design that have demonstrated an association between use of  
851 psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper

852 gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may  
853 potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have  
854 been reported when SSRIs or SNRIs are coadministered with warfarin. Patients receiving  
855 warfarin therapy should be carefully monitored when paroxetine is initiated or discontinued.

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

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

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

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

867 **Procyclidine:** Daily oral dosing of PAXIL (30 mg once daily) increased steady-state AUC<sub>0-</sub>  
868 <sub>24</sub>, C<sub>max</sub>, and C<sub>min</sub> values of procyclidine (5 mg oral once daily) by 35%, 37%, and 67%,  
869 respectively, compared to procyclidine alone at steady state. If anticholinergic effects are seen,  
870 the dose of procyclidine should be reduced.

871 **Beta-Blockers:** In a study where propranolol (80 mg twice daily) was dosed orally for  
872 18 days, the established steady-state plasma concentrations of propranolol were unaltered during  
873 coadministration with PAXIL (30 mg once daily) for the final 10 days. The effects of  
874 propranolol on paroxetine have not been evaluated (see ADVERSE REACTIONS:  
875 Postmarketing Reports).

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

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

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

885 **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** Two-year  
886 carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and  
887 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to 2.4 (mouse) and  
888 3.9 (rat) times the MRHD for major depressive disorder, social anxiety disorder, GAD, and  
889 PTSD on a mg/m<sup>2</sup> basis. Because the MRHD for major depressive disorder is slightly less than  
890 that for OCD (50 mg versus 60 mg), the doses used in these carcinogenicity studies were only  
891 2.0 (mouse) and 3.2 (rat) times the MRHD for OCD. There was a significantly greater number of

892 male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50, and 4/50 for  
893 control, low-, middle-, and high-dose groups, respectively) and a significantly increased linear  
894 trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats  
895 were not affected. Although there was a dose-related increase in the number of tumors in mice,  
896 there was no drug-related increase in the number of mice with tumors. The relevance of these  
897 findings to humans is unknown.

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

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

905 A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of  
906 15 mg/kg/day, which is 2.9 times the MRHD for major depressive disorder, social anxiety  
907 disorder, GAD, and PTSD or 2.4 times the MRHD for OCD on a mg/m<sup>2</sup> basis. Irreversible  
908 lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to  
909 52 weeks. These lesions consisted of vacuolation of epididymal tubular epithelium at  
910 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with arrested  
911 spermatogenesis at 25 mg/kg/day (9.8 and 4.9 times the MRHD for major depressive disorder,  
912 social anxiety disorder, and GAD; 8.2 and 4.1 times the MRHD for OCD and PD on a mg/m<sup>2</sup>  
913 basis).

914 **Pregnancy:** Pregnancy Category D. See WARNINGS: Usage in Pregnancy: *Teratogenic*  
915 *Effects* and *Nonteratogenic Effects*.

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

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

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

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



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

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

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

#### 947 **ADVERSE REACTIONS**

948 **Associated With Discontinuation of Treatment:** Twenty percent (1,199/6,145) of patients  
949 treated with PAXIL in worldwide clinical trials in major depressive disorder and 16.1%  
950 (84/522), 11.8% (64/542), 9.4% (44/469), 10.7% (79/735), and 11.7% (79/676) of patients  
951 treated with PAXIL in worldwide trials in social anxiety disorder, OCD, panic disorder, GAD,  
952 and PTSD, respectively, discontinued treatment due to an adverse event. The most common  
953 events ( $\geq 1\%$ ) associated with discontinuation and considered to be drug related (i.e., those events  
954 associated with dropout at a rate approximately twice or greater for PAXIL compared to placebo)  
955 included the following:  
956

	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
<b>CNS</b>												
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%	—	—
<b>Gastrointestinal</b>												
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%			—	—
<b>Other</b>												
Asthenia	1.6%	0.4%	1.9%	0.4%			2.5%	0.6%	1.8%	0.2%	1.6%	0.2%
Abnormal Ejaculation <sup>a</sup>	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 <sup>a</sup>	—		1.5%	0%							—	—
Libido Decreased							1.0%	0%			—	—

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

959 a. Incidence corrected for gender.

960

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

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

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

973 abnormal ejaculation, female genital disorders, and impotence.

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

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

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

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

997 **Major Depressive Disorder:** Table 2 enumerates adverse events that occurred at an  
998 incidence of 1% or more among paroxetine-treated patients who participated in short-term  
999 (6-week) placebo-controlled trials in which patients were dosed in a range of 20 mg to  
1000 50 mg/day. Reported adverse events were classified using a standard COSTART-based  
1001 Dictionary terminology.

1002

1003 **Table 2. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled**  
 1004 **Clinical Trials for Major Depressive Disorder<sup>a</sup>**

<b>Body System</b>	<b>Preferred Term</b>	<b>PAXIL (n = 421)</b>	<b>Placebo (n = 421)</b>
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 <sup>b</sup>	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 <sup>c,d</sup>	13%	0%
	Other Male Genital Disorders <sup>c,e</sup>	10%	0%
	Urinary Frequency	3%	1%
	Urination Disorder <sup>f</sup>	3%	0%
	Female Genital Disorders <sup>c,g</sup>	2%	0%

1005 a. Events reported by at least 1% of patients treated with PAXIL are included, except the  
 1006 following events which had an incidence on placebo  $\geq$  PAXIL: Abdominal pain, agitation,  
 1007 back pain, chest pain, CNS stimulation, fever, increased appetite, myoclonus, pharyngitis,  
 1008 postural hypotension, respiratory disorder (includes mostly “cold symptoms” or “URI”),  
 1009 trauma, and vomiting.

1010 b. Includes mostly “lump in throat” and “tightness in throat.”

- 1011 c. Percentage corrected for gender.
- 1012 d. Mostly “ejaculatory delay.”
- 1013 e. Includes “anorgasmia,” “erectile difficulties,” “delayed ejaculation/orgasm,” and “sexual
- 1014 dysfunction,” and “impotence.”
- 1015 f. Includes mostly “difficulty with micturition” and “urinary hesitancy.”
- 1016 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<sup>a</sup>**

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 <sup>b</sup>	23%	1%	21%	1%	28%	1%
	Dysmenorrhea	—	—	—	—	5%	4%
	Female Genital Disorder <sup>b</sup>	3%	0%	9%	1%	9%	1%
	Impotence <sup>b</sup>	8%	1%	5%	0%	5%	1%
	Urinary Frequency	3%	1%	2%	0%	—	—
	Urination Impaired	3%	0%	—	—	—	—
	Urinary Tract Infection	2%	1%	2%	1%	—	—

1030 a. Events reported by at least 2% of OCD, panic disorder, and social anxiety disorder in patients  
1031 treated with PAXIL are included, except the following events which had an incidence on  
1032 placebo  $\geq$  PAXIL: [OCD]: Abdominal pain, agitation, anxiety, back pain, cough increased,  
1033 depression, headache, hyperkinesia, infection, paresthesia, pharyngitis, respiratory disorder,  
1034 rhinitis, and sinusitis. [panic disorder]: Abnormal dreams, abnormal vision, chest pain, cough  
1035 increased, depersonalization, depression, dysmenorrhea, dyspepsia, flu syndrome, headache,

1036 infection, myalgia, nervousness, palpitation, paresthesia, pharyngitis, rash, respiratory  
1037 disorder, sinusitis, taste perversion, trauma, urination impaired, and vasodilation. [social  
1038 anxiety disorder]: Abdominal pain, depression, headache, infection, respiratory disorder, and  
1039 sinusitis.

1040 b. Percentage corrected for gender.

1041

1042 **Generalized Anxiety Disorder and Posttraumatic Stress Disorder:** Table 4  
1043 enumerates adverse events that occurred at a frequency of 2% or more among GAD patients on  
1044 PAXIL who participated in placebo-controlled trials of 8-weeks duration in which patients were  
1045 dosed in a range of 10 mg/day to 50 mg/day or among PTSD patients on PAXIL who  
1046 participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a  
1047 range of 20 mg/day to 50 mg/day.

1048

1049 **Table 4. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled**  
 1050 **Clinical Trials for Generalized Anxiety Disorder and Posttraumatic Stress Disorder<sup>a</sup>**

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 <sup>b</sup>	25%	2%	13%	2%
	Female Genital Disorder <sup>b</sup>	4%	1%	5%	1%
	Impotence <sup>b</sup>	4%	3%	9%	1%

- 1051 a. Events reported by at least 2% of GAD and PTSD in patients treated with PAXIL are  
 1052 included, except the following events which had an incidence on placebo  $\geq$  PAXIL [GAD]:  
 1053 Abdominal pain, back pain, trauma, dyspepsia, myalgia, and pharyngitis. [PTSD]: Back pain,  
 1054 headache, anxiety, depression, nervousness, respiratory disorder, pharyngitis, and sinusitis.  
 1055 b. Percentage corrected for gender.

1056  
 1057 **Dose Dependency of Adverse Events:** A comparison of adverse event rates in a  
 1058 fixed-dose study comparing 10, 20, 30, and 40 mg/day of PAXIL with placebo in the treatment  
 1059 of major depressive disorder revealed a clear dose dependency for some of the more common  
 1060 adverse events associated with use of PAXIL, as shown in Table 5:



1061  
1062  
1063

**Table 5. Treatment-Emergent Adverse Experience Incidence in a Dose-Comparison Trial in the Treatment of Major Depressive Disorder<sup>a</sup>**

Body System/Preferred Term	Placebo n = 51	PAXIL			
		10 mg n = 102	20 mg n = 104	30 mg n = 101	40 mg n = 102
<b>Body as a Whole</b>					
Asthenia	0.0%	2.9%	10.6%	13.9%	12.7%
<b>Dermatology</b>					
Sweating	2.0%	1.0%	6.7%	8.9%	11.8%
<b>Gastrointestinal</b>					
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%
<b>Nervous System</b>					
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%
<b>Special Senses</b>					
Blurred Vision	2.0%	2.9%	2.9%	2.0%	7.8%
<b>Urogenital System</b>					
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%

1064 a. Rule for including adverse events in table: Incidence at least 5% for 1 of paroxetine groups  
1065 and  $\geq$  twice the placebo incidence for at least 1 paroxetine group.  
1066

1067 In a fixed-dose study comparing placebo and 20, 40, and 60 mg of PAXIL in the treatment of  
1068 OCD, there was no clear relationship between adverse events and the dose of PAXIL to which  
1069 patients were assigned. No new adverse events were observed in the group treated with 60 mg of  
1070 PAXIL compared to any of the other treatment groups.

1071 In a fixed-dose study comparing placebo and 10, 20, and 40 mg of PAXIL in the treatment of  
1072 panic disorder, there was no clear relationship between adverse events and the dose of PAXIL to  
1073 which patients were assigned, except for asthenia, dry mouth, anxiety, libido decreased, tremor,  
1074 and abnormal ejaculation. In flexible-dose studies, no new adverse events were observed in  
1075 patients receiving 60 mg of PAXIL compared to any of the other treatment groups.

1076 In a fixed-dose study comparing placebo and 20, 40, and 60 mg of PAXIL in the treatment of  
1077 social anxiety disorder, for most of the adverse events, there was no clear relationship between

1078 adverse events and the dose of PAXIL to which patients were assigned.

1079 In a fixed-dose study comparing placebo and 20 and 40 mg of PAXIL in the treatment of  
1080 generalized anxiety disorder, for most of the adverse events, there was no clear relationship  
1081 between adverse events and the dose of PAXIL to which patients were assigned, except for the  
1082 following adverse events: Asthenia, constipation, and abnormal ejaculation.

1083 In a fixed-dose study comparing placebo and 20 and 40 mg of PAXIL in the treatment of  
1084 posttraumatic stress disorder, for most of the adverse events, there was no clear relationship  
1085 between adverse events and the dose of PAXIL to which patients were assigned, except for  
1086 impotence and abnormal ejaculation.

1087 **Adaptation to Certain Adverse Events:** Over a 4- to 6-week period, there was evidence  
1088 of adaptation to some adverse events with continued therapy (e.g., nausea and dizziness), but less  
1089 to other effects (e.g., dry mouth, somnolence, and asthenia).

1090 **Male and Female Sexual Dysfunction With SSRIs:** Although changes in sexual desire,  
1091 sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric  
1092 disorder, they may also be a consequence of pharmacologic treatment. In particular, some  
1093 evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward  
1094 sexual experiences.

1095 Reliable estimates of the incidence and severity of untoward experiences involving sexual  
1096 desire, performance, and satisfaction are difficult to obtain, however, in part because patients and  
1097 physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of  
1098 untoward sexual experience and performance cited in product labeling, are likely to  
1099 underestimate their actual incidence.

1100 In placebo-controlled clinical trials involving more than 3,200 patients, the ranges for the  
1101 reported incidence of sexual side effects in males and females with major depressive disorder,  
1102 OCD, panic disorder, social anxiety disorder, GAD, and PTSD are displayed in Table 6.

1103

1104 **Table 6. Incidence of Sexual Adverse Events in Controlled Clinical Trials**

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

1105

1106 There are no adequate and well-controlled studies examining sexual dysfunction with  
1107 paroxetine treatment.

1108 Paroxetine treatment has been associated with several cases of priapism. In those cases with a  
1109 known outcome, patients recovered without sequelae.

1110 While it is difficult to know the precise risk of sexual dysfunction associated with the use of

1111 SSRIs, physicians should routinely inquire about such possible side effects.

1112 **Weight and Vital Sign Changes:** Significant weight loss may be an undesirable result of  
1113 treatment with PAXIL for some patients but, on average, patients in controlled trials had minimal  
1114 (about 1 pound) weight loss versus smaller changes on placebo and active control. No significant  
1115 changes in vital signs (systolic and diastolic blood pressure, pulse and temperature) were  
1116 observed in patients treated with PAXIL in controlled clinical trials.

1117 **ECG Changes:** In an analysis of ECGs obtained in 682 patients treated with PAXIL and  
1118 415 patients treated with placebo in controlled clinical trials, no clinically significant changes  
1119 were seen in the ECGs of either group.

1120 **Liver Function Tests:** In placebo-controlled clinical trials, patients treated with PAXIL  
1121 exhibited abnormal values on liver function tests at no greater rate than that seen in  
1122 placebo-treated patients. In particular, the PAXIL-versus-placebo comparisons for alkaline  
1123 phosphatase, SGOT, SGPT, and bilirubin revealed no differences in the percentage of patients  
1124 with marked abnormalities.

1125 **Hallucinations:** In pooled clinical trials of immediate-release paroxetine hydrochloride,  
1126 hallucinations were observed in 22 of 9089 patients receiving drug and 4 of 3187 patients  
1127 receiving placebo.

1128 **Other Events Observed During the Premarketing Evaluation of PAXIL:** During its  
1129 premarketing assessment in major depressive disorder, multiple doses of PAXIL were  
1130 administered to 6,145 patients in phase 2 and 3 studies. The conditions and duration of exposure  
1131 to PAXIL varied greatly and included (in overlapping categories) open and double-blind studies,  
1132 uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose, and titration  
1133 studies. During premarketing clinical trials in OCD, panic disorder, social anxiety disorder,  
1134 generalized anxiety disorder, and posttraumatic stress disorder, 542, 469, 522, 735, and 676  
1135 patients, respectively, received multiple doses of PAXIL. Untoward events associated with this  
1136 exposure were recorded by clinical investigators using terminology of their own choosing.  
1137 Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals  
1138 experiencing adverse events without first grouping similar types of untoward events into a  
1139 smaller number of standardized event categories.

1140 In the tabulations that follow, reported adverse events were classified using a standard  
1141 COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the  
1142 proportion of the 9,089 patients exposed to multiple doses of PAXIL who experienced an event  
1143 of the type cited on at least 1 occasion while receiving PAXIL. All reported events are included  
1144 except those already listed in Tables 2 to 5, those reported in terms so general as to be  
1145 uninformative and those events where a drug cause was remote. It is important to emphasize that  
1146 although the events reported occurred during treatment with paroxetine, they were not  
1147 necessarily caused by it.

1148 Events are further categorized by body system and listed in order of decreasing frequency  
1149 according to the following definitions: Frequent adverse events are those occurring on 1 or more  
1150 occasions in at least 1/100 patients (only those not already listed in the tabulated results from

1151 placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in  
1152 1/100 to 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients. Events  
1153 of major clinical importance are also described in the PRECAUTIONS section.

1154 **Body as a Whole:** *Infrequent:* Allergic reaction, chills, face edema, malaise, neck pain;  
1155 *rare:* Adrenergic syndrome, cellulitis, moniliasis, neck rigidity, pelvic pain, peritonitis, sepsis,  
1156 ulcer.

1157 **Cardiovascular System:** *Frequent:* Hypertension, tachycardia; *infrequent:* Bradycardia,  
1158 hematoma, hypotension, migraine, postural hypotension, syncope; *rare:* Angina pectoris,  
1159 arrhythmia nodal, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular  
1160 accident, congestive heart failure, heart block, low cardiac output, myocardial infarct, myocardial  
1161 ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis,  
1162 thrombosis, varicose vein, vascular headache, ventricular extrasystoles.

1163 **Digestive System:** *Infrequent:* Bruxism, colitis, dysphagia, eructation, gastritis,  
1164 gastroenteritis, gingivitis, glossitis, increased salivation, liver function tests abnormal, rectal  
1165 hemorrhage, ulcerative stomatitis; *rare:* Aphthous stomatitis, bloody diarrhea, bulimia,  
1166 cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal  
1167 incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, intestinal obstruction,  
1168 jaundice, melena, mouth ulceration, peptic ulcer, salivary gland enlargement, sialadenitis,  
1169 stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries.

1170 **Endocrine System:** *Rare:* Diabetes mellitus, goiter, hyperthyroidism, hypothyroidism,  
1171 thyroiditis.

1172 **Hemic and Lymphatic Systems:** *Infrequent:* Anemia, leukopenia, lymphadenopathy,  
1173 purpura; *rare:* Abnormal erythrocytes, basophilia, bleeding time increased, eosinophilia,  
1174 hypochromic anemia, iron deficiency anemia, leukocytosis, lymphedema, abnormal  
1175 lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia,  
1176 thrombocythemia, thrombocytopenia.

1177 **Metabolic and Nutritional:** *Frequent:* Weight gain; *infrequent:* Edema, peripheral edema,  
1178 SGOT increased, SGPT increased, thirst, weight loss; *rare:* Alkaline phosphatase increased,  
1179 bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, gamma  
1180 globulins increased, gout, hypercalcemia, hypercholesteremia, hyperglycemia, hyperkalemia,  
1181 hyperphosphatemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, ketosis, lactic  
1182 dehydrogenase increased, non-protein nitrogen (NPN) increased.

1183 **Musculoskeletal System:** *Frequent:* Arthralgia; *infrequent:* Arthritis, arthrosis; *rare:*  
1184 Bursitis, myositis, osteoporosis, generalized spasm, tenosynovitis, tetany.

1185 **Nervous System:** *Frequent:* Emotional lability, vertigo; *infrequent:* Abnormal thinking,  
1186 alcohol abuse, ataxia, dystonia, dyskinesia, euphoria, hallucinations, hostility, hypertonia,  
1187 hypesthesia, hypokinesia, incoordination, lack of emotion, libido increased, manic reaction,  
1188 neurosis, paralysis, paranoid reaction; *rare:* Abnormal gait, akinesia, antisocial reaction, aphasia,  
1189 choreoathetosis, circumoral paresthesias, convulsion, delirium, delusions, diplopia, drug  
1190 dependence, dysarthria, extrapyramidal syndrome, fasciculations, grand mal convulsion,

1191 hyperalgesia, hysteria, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy,  
1192 nystagmus, peripheral neuritis, psychotic depression, psychosis, reflexes decreased, reflexes  
1193 increased, stupor, torticollis, trismus, withdrawal syndrome.

1194 **Respiratory System:** *Infrequent:* Asthma, bronchitis, dyspnea, epistaxis, hyperventilation,  
1195 pneumonia, respiratory flu; *rare:* Emphysema, hemoptysis, hiccups, lung fibrosis, pulmonary  
1196 edema, sputum increased, stridor, voice alteration.

1197 **Skin and Appendages:** *Frequent:* Pruritus; *infrequent:* Acne, alopecia, contact dermatitis,  
1198 dry skin, ecchymosis, eczema, herpes simplex, photosensitivity, urticaria; *rare:* Angioedema,  
1199 erythema nodosum, erythema multiforme, exfoliative dermatitis, fungal dermatitis, furunculosis;  
1200 herpes zoster, hirsutism, maculopapular rash, seborrhea, skin discoloration, skin hypertrophy,  
1201 skin ulcer, sweating decreased, vesiculobullous rash.

1202 **Special Senses:** *Frequent:* Tinnitus; *infrequent:* Abnormality of accommodation,  
1203 conjunctivitis, ear pain, eye pain, keratoconjunctivitis, mydriasis, otitis media; *rare:* Amblyopia,  
1204 anisocoria, blepharitis, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, eye  
1205 hemorrhage, glaucoma, hyperacusis, night blindness, otitis externa, parosmia, photophobia,  
1206 ptosis, retinal hemorrhage, taste loss, visual field defect.

1207 **Urogenital System:** *Infrequent:* Amenorrhea, breast pain, cystitis, dysuria, hematuria,  
1208 menorrhagia, nocturia, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency,  
1209 vaginitis; *rare:* Abortion, breast atrophy, breast enlargement, endometrial disorder, epididymitis,  
1210 female lactation, fibrocystic breast, kidney calculus, kidney pain, leukorrhea, mastitis,  
1211 metrorrhagia, nephritis, oliguria, salpingitis, urethritis, urinary casts, uterine spasm, urolith,  
1212 vaginal hemorrhage, vaginal moniliasis.

1213 **Postmarketing Reports:** Voluntary reports of adverse events in patients taking PAXIL that  
1214 have been received since market introduction and not listed above that may have no causal  
1215 relationship with the drug include acute pancreatitis, elevated liver function tests (the most  
1216 severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated  
1217 with severe liver dysfunction), Guillain-Barré syndrome, Stevens-Johnson syndrome, toxic  
1218 epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive  
1219 of prolactinemia and galactorrhea; extrapyramidal symptoms which have included akathisia,  
1220 bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been  
1221 associated with concomitant use of pimozide; tremor and trismus; status epilepticus, acute renal  
1222 failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic  
1223 neuritis, porphyria, restless legs syndrome (RLS), ventricular fibrillation, ventricular tachycardia  
1224 (including torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired  
1225 hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and  
1226 agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura). There has been  
1227 a case report of an elevated phenytoin level after 4 weeks of PAXIL and phenytoin  
1228 coadministration. There has been a case report of severe hypotension when PAXIL was added to  
1229 chronic metoprolol treatment.

1230 **DRUG ABUSE AND DEPENDENCE**

1231 **Controlled Substance Class:** PAXIL is not a controlled substance.

1232 **Physical and Psychologic Dependence:** PAXIL has not been systematically studied in  
1233 animals or humans for its potential for abuse, tolerance or physical dependence. While the  
1234 clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were  
1235 not systematic and it is not possible to predict on the basis of this limited experience the extent to  
1236 which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently,  
1237 patients should be evaluated carefully for history of drug abuse, and such patients should be  
1238 observed closely for signs of misuse or abuse of PAXIL (e.g., development of tolerance,  
1239 incrementations of dose, drug-seeking behavior).

1240 **OVERDOSAGE**

1241 **Human Experience:** Since the introduction of PAXIL in the United States, 342 spontaneous  
1242 cases of deliberate or accidental overdosage during paroxetine treatment have been reported  
1243 worldwide (circa 1999). These include overdoses with paroxetine alone and in combination with  
1244 other substances. Of these, 48 cases were fatal and of the fatalities, 17 appeared to involve  
1245 paroxetine alone. Eight fatal cases that documented the amount of paroxetine ingested were  
1246 generally confounded by the ingestion of other drugs or alcohol or the presence of significant  
1247 comorbid conditions. Of 145 non-fatal cases with known outcome, most recovered without  
1248 sequelae. The largest known ingestion involved 2,000 mg of paroxetine (33 times the maximum  
1249 recommended daily dose) in a patient who recovered.

1250 Commonly reported adverse events associated with paroxetine overdosage include  
1251 somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other  
1252 notable signs and symptoms observed with overdoses involving paroxetine (alone or with other  
1253 substances) include mydriasis, convulsions (including status epilepticus), ventricular  
1254 dysrhythmias (including torsade de pointes), hypertension, aggressive reactions, syncope,  
1255 hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction  
1256 (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin  
1257 syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

1258 **Overdosage Management:** No specific antidotes for paroxetine are known. Treatment  
1259 should consist of those general measures employed in the management of overdosage with any  
1260 drugs effective in the treatment of major depressive disorder.

1261 Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital  
1262 signs. General supportive and symptomatic measures are also recommended. Induction of emesis  
1263 is not recommended. Due to the large volume of distribution of this drug, forced diuresis,  
1264 dialysis, hemoperfusion, or exchange transfusion are unlikely to be of benefit.

1265 A specific caution involves patients who are taking or have recently taken paroxetine who  
1266 might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the  
1267 parent tricyclic and/or an active metabolite may increase the possibility of clinically significant  
1268 sequelae and extend the time needed for close medical observation (see PRECAUTIONS: *Drugs*

1269 *Metabolized by Cytochrome CYP2D6).*

1270 In managing overdose, consider the possibility of multiple drug involvement. The physician  
1271 should consider contacting a poison control center for additional information on the treatment of  
1272 any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians'*  
1273 *Desk Reference* (PDR).

## 1274 **DOSAGE AND ADMINISTRATION**

1275 **Major Depressive Disorder: Usual Initial Dosage:** PAXIL should be administered as a  
1276 single daily dose with or without food, usually in the morning. The recommended initial dose is  
1277 20 mg/day. Patients were dosed in a range of 20 to 50 mg/day in the clinical trials demonstrating  
1278 the effectiveness of PAXIL in the treatment of major depressive disorder. As with all drugs  
1279 effective in the treatment of major depressive disorder, the full effect may be delayed. Some  
1280 patients not responding to a 20-mg dose may benefit from dose increases, in 10-mg/day  
1281 increments, up to a maximum of 50 mg/day. Dose changes should occur at intervals of at least  
1282 1 week.

1283 **Maintenance Therapy:** There is no body of evidence available to answer the question of  
1284 how long the patient treated with PAXIL should remain on it. It is generally agreed that acute  
1285 episodes of major depressive disorder require several months or longer of sustained  
1286 pharmacologic therapy. Whether the dose needed to induce remission is identical to the dose  
1287 needed to maintain and/or sustain euthymia is unknown.

1288 Systematic evaluation of the efficacy of PAXIL has shown that efficacy is maintained for  
1289 periods of up to 1 year with doses that averaged about 30 mg.

1290 **Obsessive Compulsive Disorder: Usual Initial Dosage:** PAXIL should be administered  
1291 as a single daily dose with or without food, usually in the morning. The recommended dose of  
1292 PAXIL in the treatment of OCD is 40 mg daily. Patients should be started on 20 mg/day and the  
1293 dose can be increased in 10-mg/day increments. Dose changes should occur at intervals of at  
1294 least 1 week. Patients were dosed in a range of 20 to 60 mg/day in the clinical trials  
1295 demonstrating the effectiveness of PAXIL in the treatment of OCD. The maximum dosage  
1296 should not exceed 60 mg/day.

1297 **Maintenance Therapy:** Long-term maintenance of efficacy was demonstrated in a 6-month  
1298 relapse prevention trial. In this trial, patients with OCD assigned to paroxetine demonstrated a  
1299 lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY:  
1300 Clinical Trials). OCD is a chronic condition, and it is reasonable to consider continuation for a  
1301 responding patient. Dosage adjustments should be made to maintain the patient on the lowest  
1302 effective dosage, and patients should be periodically reassessed to determine the need for  
1303 continued treatment.

1304 **Panic Disorder: Usual Initial Dosage:** PAXIL should be administered as a single daily dose  
1305 with or without food, usually in the morning. The target dose of PAXIL in the treatment of panic  
1306 disorder is 40 mg/day. Patients should be started on 10 mg/day. Dose changes should occur in  
1307 10-mg/day increments and at intervals of at least 1 week. Patients were dosed in a range of 10 to

1308 60 mg/day in the clinical trials demonstrating the effectiveness of PAXIL. The maximum dosage  
1309 should not exceed 60 mg/day.

1310 **Maintenance Therapy:** Long-term maintenance of efficacy was demonstrated in a 3-month  
1311 relapse prevention trial. In this trial, patients with panic disorder assigned to paroxetine  
1312 demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL  
1313 PHARMACOLOGY: Clinical Trials). Panic disorder is a chronic condition, and it is reasonable  
1314 to consider continuation for a responding patient. Dosage adjustments should be made to  
1315 maintain the patient on the lowest effective dosage, and patients should be periodically  
1316 reassessed to determine the need for continued treatment.

1317 **Social Anxiety Disorder: Usual Initial Dosage:** PAXIL should be administered as a single  
1318 daily dose with or without food, usually in the morning. The recommended and initial dosage is  
1319 20 mg/day. In clinical trials the effectiveness of PAXIL was demonstrated in patients dosed in a  
1320 range of 20 to 60 mg/day. While the safety of PAXIL has been evaluated in patients with social  
1321 anxiety disorder at doses up to 60 mg/day, available information does not suggest any additional  
1322 benefit for doses above 20 mg/day (see CLINICAL PHARMACOLOGY: Clinical Trials).

1323 **Maintenance Therapy:** There is no body of evidence available to answer the question of  
1324 how long the patient treated with PAXIL should remain on it. Although the efficacy of PAXIL  
1325 beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials, social anxiety  
1326 disorder is recognized as a chronic condition, and it is reasonable to consider continuation of  
1327 treatment for a responding patient. Dosage adjustments should be made to maintain the patient  
1328 on the lowest effective dosage, and patients should be periodically reassessed to determine the  
1329 need for continued treatment.

1330 **Generalized Anxiety Disorder: Usual Initial Dosage:** PAXIL should be administered as a  
1331 single daily dose with or without food, usually in the morning. In clinical trials the effectiveness  
1332 of PAXIL was demonstrated in patients dosed in a range of 20 to 50 mg/day. The recommended  
1333 starting dosage and the established effective dosage is 20 mg/day. There is not sufficient  
1334 evidence to suggest a greater benefit to doses higher than 20 mg/day. Dose changes should occur  
1335 in 10 mg/day increments and at intervals of at least 1 week.

1336 **Maintenance Therapy:** Systematic evaluation of continuing PAXIL for periods of up to  
1337 24 weeks in patients with Generalized Anxiety Disorder who had responded while taking PAXIL  
1338 during an 8-week acute treatment phase has demonstrated a benefit of such maintenance (see  
1339 CLINICAL PHARMACOLOGY: Clinical Trials). Nevertheless, patients should be periodically  
1340 reassessed to determine the need for maintenance treatment.

1341 **Posttraumatic Stress Disorder: Usual Initial Dosage:** PAXIL should be administered as  
1342 a single daily dose with or without food, usually in the morning. The recommended starting  
1343 dosage and the established effective dosage is 20 mg/day. In 1 clinical trial, the effectiveness of  
1344 PAXIL was demonstrated in patients dosed in a range of 20 to 50 mg/day. However, in a fixed  
1345 dose study, there was not sufficient evidence to suggest a greater benefit for a dose of 40 mg/day  
1346 compared to 20 mg/day. Dose changes, if indicated, should occur in 10 mg/day increments and at  
1347 intervals of at least 1 week.



1348 **Maintenance Therapy:** There is no body of evidence available to answer the question of  
1349 how long the patient treated with PAXIL should remain on it. Although the efficacy of PAXIL  
1350 beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials, PTSD is  
1351 recognized as a chronic condition, and it is reasonable to consider continuation of treatment for a  
1352 responding patient. Dosage adjustments should be made to maintain the patient on the lowest  
1353 effective dosage, and patients should be periodically reassessed to determine the need for  
1354 continued treatment.

1355 **Special Populations: Treatment of Pregnant Women During the Third Trimester:**

1356 Neonates exposed to PAXIL and other SSRIs or SNRIs, late in the third trimester have  
1357 developed complications requiring prolonged hospitalization, respiratory support, and tube  
1358 feeding (see WARNINGS: Usage in Pregnancy). When treating pregnant women with paroxetine  
1359 during the third trimester, the physician should carefully consider the potential risks and benefits  
1360 of treatment. The physician may consider tapering paroxetine in the third trimester.

1361 **Dosage for Elderly or Debilitated Patients, and Patients With Severe Renal or**

1362 **Hepatic Impairment:** The recommended initial dose is 10 mg/day for elderly patients,  
1363 debilitated patients, and/or patients with severe renal or hepatic impairment. Increases may be  
1364 made if indicated. Dosage should not exceed 40 mg/day.

1365 **Switching Patients to or From a Monoamine Oxidase Inhibitor Antidepressant:** At

1366 least 14 days should elapse between discontinuation of an MAOI intended to treat depression and  
1367 initiation of therapy with PAXIL. Conversely, at least 14 days should be allowed after stopping  
1368 PAXIL before starting an MAOI antidepressant (see CONTRAINDICATIONS).

1369 **Use of PAXIL With Reversible MAOIs Such as Linezolid or Methylene Blue:** Do not

1370 start PAXIL in a patient who is being treated with linezolid or methylene blue because there is  
1371 increased risk of serotonin syndrome or NMS-like reactions. In a patient who requires more  
1372 urgent treatment of a psychiatric condition, non-pharmacological interventions, including  
1373 hospitalization, should be considered (see CONTRAINDICATIONS). In some cases, a patient  
1374 receiving therapy with PAXIL may require urgent treatment with linezolid or methylene blue. If  
1375 acceptable alternatives to linezolid or methylene blue treatment are not available and the  
1376 potential benefits of linezolid or methylene blue treatment are judged to outweigh the risks of  
1377 serotonin syndrome or NMS-like reactions in a particular patient, PAXIL should be stopped  
1378 promptly, and linezolid or methylene blue can be administered. The patient should be monitored  
1379 for symptoms of serotonin syndrome or NMS-like reactions for 2 weeks or until 24 hours after  
1380 the last dose of linezolid or methylene blue, whichever comes first. Therapy with PAXIL may be  
1381 resumed 24 hours after the last dose of linezolid or methylene blue (see WARNINGS).

1382 **Discontinuation of Treatment With PAXIL:** Symptoms associated with discontinuation of

1383 PAXIL have been reported (see PRECAUTIONS: *Discontinuation of Treatment With PAXIL*).  
1384 Patients should be monitored for these symptoms when discontinuing treatment, regardless of the  
1385 indication for which PAXIL is being prescribed. A gradual reduction in the dose rather than  
1386 abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a  
1387 decrease in the dose or upon discontinuation of treatment, then resuming the previously

1388 prescribed dose may be considered. Subsequently, the physician may continue decreasing the  
1389 dose but at a more gradual rate.

1390 **NOTE: SHAKE SUSPENSION WELL BEFORE USING.**

1391 **HOW SUPPLIED**

1392 **Tablets:** Film-coated, modified-oval as follows:

1393 10-mg yellow, scored tablets engraved on the front with PAXIL and on the back with 10.

1394 NDC 0029-3210-13 Bottles of 30

1395 20-mg pink, scored tablets engraved on the front with PAXIL and on the back with 20.

1396 NDC 0029-3211-13 Bottles of 30

1397 30-mg blue tablets engraved on the front with PAXIL and on the back with 30.

1398 NDC 0029-3212-13 Bottles of 30

1399 40-mg green tablets engraved on the front with PAXIL and on the back with 40.

1400 NDC 0029-3213-13 Bottles of 30

1401 Store tablets between 15° and 30°C (59° and 86°F).

1402 **Oral Suspension:** Orange-colored, orange-flavored, 10 mg/5 mL, in white bottles containing  
1403 250 mL.

1404 NDC 0029-3215-48

1405 Store suspension at or below 25°C (77°F).

1406 PAXIL is a registered trademark of GlaxoSmithKline.

1407



1408

1409

GlaxoSmithKline  
Research Triangle Park, NC 27709

1410 ©2011, GlaxoSmithKline. All rights reserved.

1411

1412 Month 2011

PXL:XXPI

1413

1414  
1415 **Medication Guide**

1416 **PAXIL® (PAX-il)**

1417 **(paroxetine hydrochloride)**

1418 **Tablets and Oral Suspension**

1419  
1420 Read the Medication Guide that comes with PAXIL before you start taking it and each time you  
1421 get a refill. There may be new information. This Medication Guide does not take the place of  
1422 talking to your healthcare provider about your medical condition or treatment. Talk with your  
1423 healthcare provider if there is something you do not understand or want to learn more about.

1424  
1425 **What is the most important information I should know about PAXIL?**

1426 PAXIL and other antidepressant medicines may cause serious side effects, including:

1427 **1. Suicidal thoughts or actions:**

- 1428 • **PAXIL and other antidepressant medicines may increase suicidal thoughts or**  
1429 **actions** in some children, teenagers, or young adults within the **first few months of**  
1430 **treatment or when the dose is changed.**
- 1431 • Depression or other serious mental illnesses are the most important causes of suicidal  
1432 thoughts or actions.
- 1433 • Watch for these changes and call your healthcare provider right away if you notice:
- 1434 • New or sudden changes in mood, behavior, actions, thoughts, or feelings, especially  
1435 if severe.
- 1436 • Pay particular attention to such changes when PAXIL is started or when the dose is  
1437 changed.

1438 Keep all follow-up visits with your healthcare provider and call between visits if you are worried  
1439 about symptoms.

1440 **Call your healthcare provider right away if you have any of the following symptoms,**  
1441 **or call 911 if an emergency, especially if they are new, worse, or worry you:**

- 1442 • attempts to commit suicide
- 1443 • acting on dangerous impulses
- 1444 • acting aggressive or violent
- 1445 • thoughts about suicide or dying
- 1446 • new or worse depression
- 1447 • new or worse anxiety or panic attacks
- 1448 • feeling agitated, restless, angry, or irritable
- 1449 • trouble sleeping
- 1450 • an increase in activity or talking more than what is normal for you
- 1451 • other unusual changes in behavior or mood

1452 **Call your healthcare provider right away if you have any of the following symptoms, or call**

- 1453 **911 if an emergency. PAXIL may be associated with these serious side effects:**
- 1454 **2. Serotonin Syndrome or Neuroleptic Malignant Syndrome-like reactions. This**
- 1455 **condition can be life-threatening and may include:**
- 1456 • agitation, hallucinations, coma, or other changes in mental status
- 1457 • coordination problems or muscle twitching (overactive reflexes)
- 1458 • racing heartbeat, high or low blood pressure
- 1459 • sweating or fever
- 1460 • nausea, vomiting, or diarrhea
- 1461 • muscle rigidity
- 1462 **3. Severe allergic reactions:**
- 1463 • trouble breathing
- 1464 • swelling of the face, tongue, eyes, or mouth
- 1465 • rash, itchy welts (hives), or blisters, alone or with fever or joint pain
- 1466 **4. Abnormal bleeding:** PAXIL and other antidepressant medicines may increase your risk of
- 1467 bleeding or bruising, especially if you take the blood thinner warfarin (Coumadin<sup>®</sup>,
- 1468 Jantoven<sup>®</sup>), a non-steroidal anti-inflammatory drug (NSAIDs, like ibuprofen or naproxen),
- 1469 or aspirin.
- 1470 **5. Seizures or convulsions**
- 1471 **6. Manic episodes:**
- 1472 • greatly increased energy
- 1473 • severe trouble sleeping
- 1474 • racing thoughts
- 1475 • reckless behavior
- 1476 • unusually grand ideas
- 1477 • excessive happiness or irritability
- 1478 • talking more or faster than usual
- 1479 **7. Changes in appetite or weight.** Children and adolescents should have height and weight
- 1480 monitored during treatment.
- 1481 **8. Low salt (sodium) levels in the blood.** Elderly people may be at greater risk for this.
- 1482 Symptoms may include:
- 1483 • headache
- 1484 • weakness or feeling unsteady
- 1485 • confusion, problems concentrating or thinking, or memory problems
- 1486 **Do not stop PAXIL without first talking to your healthcare provider.** Stopping PAXIL too
- 1487 quickly may cause serious symptoms including:
- 1488 • anxiety, irritability, high or low mood, feeling restless, or changes in sleep habits
- 1489 • headache, sweating, nausea, dizziness
- 1490 • electric shock-like sensations, shaking, confusion
- 1491
- 1492 **What is PAXIL?**

1493 PAXIL is a prescription medicine used to treat depression. It is important to talk with your  
1494 healthcare provider about the risks of treating depression and also the risks of not treating it. You  
1495 should discuss all treatment choices with your healthcare provider. PAXIL is also used to treat:

- 1496 • Major Depressive Disorder (MDD)
- 1497 • Obsessive Compulsive Disorder (OCD)
- 1498 • Panic Disorder
- 1499 • Social Anxiety Disorder
- 1500 • Generalized Anxiety Disorder (GAD)
- 1501 • Posttraumatic Stress Disorder (PTSD)

1502 Talk to your healthcare provider if you do not think that your condition is getting better with  
1503 treatment using PAXIL.

1504

### 1505 **Who should not take PAXIL?**

1506 Do not take PAXIL if you:

- 1507 • are allergic to paroxetine or any of the ingredients in PAXIL. See the end of this Medication  
1508 Guide for a complete list of ingredients in PAXIL.
- 1509 • take a monoamine oxidase inhibitor (MAOI). Ask your healthcare provider or pharmacist if  
1510 you are not sure if you take an MAOI, including the antibiotic linezolid.
- 1511 • Do not take an MAOI within 2 weeks of stopping PAXIL unless directed to do so by your  
1512 physician.
- 1513 • Do not start PAXIL if you stopped taking an MAOI in the last 2 weeks unless directed to do  
1514 so by your physician.
- 1515 • **People who take PAXIL close in time to an MAOI may have serious or even life-**  
1516 **threatening side effects. Get medical help right away if you have any of these**  
1517 **symptoms:**
  - 1518 • high fever
  - 1519 • uncontrolled muscle spasms
  - 1520 • stiff muscles
  - 1521 • rapid changes in heart rate or blood pressure
  - 1522 • confusion
  - 1523 • loss of consciousness (pass out)
- 1524 • **take MELLARIL<sup>®</sup> (thioridazine). Do not take MELLARIL<sup>®</sup> together with PAXIL**  
1525 **because this can cause serious heart rhythm problems or sudden death.**
- 1526 • **take the antipsychotic medicine pimozide (ORAP<sup>®</sup>) because this can cause serious heart**  
1527 **problems.**

1528

1529 **What should I tell my healthcare provider before taking PAXIL? Ask if you are not sure.**

1530 Before starting PAXIL, tell your healthcare provider if you:

- 1531 • **are pregnant, may be pregnant, or plan to become pregnant.** There is a possibility that  
1532 PAXIL may harm your unborn baby, including an increased risk of birth defects, particularly  
1533 heart defects. Other risks may include a serious condition in which there is not enough  
1534 oxygen in the baby’s blood. Your baby may also have certain other symptoms shortly after  
1535 birth. Premature births have also been reported in some women who used PAXIL during  
1536 pregnancy.
- 1537 • **are breastfeeding.** PAXIL passes into your milk. Talk to your healthcare provider about the  
1538 best way to feed your baby while taking PAXIL.
- 1539 • are taking certain drugs such as:
- 1540 • triptans used to treat migraine headache
  - 1541 • other antidepressants (SSRIs, SNRIs, tricyclics, or lithium) or antipsychotics
  - 1542 • drugs that affect serotonin, such as lithium, tramadol, tryptophan, St. John’s wort
  - 1543 • certain drugs used to treat irregular heart beats
  - 1544 • certain drugs used to treat schizophrenia
  - 1545 • certain drugs used to treat HIV infection
  - 1546 • certain drugs that affect the blood, such as warfarin, aspirin, and ibuprofen
  - 1547 • certain drugs used to treat epilepsy
  - 1548 • atomoxetine
  - 1549 • cimetidine
  - 1550 • fentanyl
  - 1551 • metoprolol
  - 1552 • pimozide
  - 1553 • procyclidine
  - 1554 • tamoxifen
- 1555 • have liver problems
- 1556 • have kidney problems
- 1557 • have heart problems
- 1558 • have or had seizures or convulsions
- 1559 • have bipolar disorder or mania
- 1560 • have low sodium levels in your blood
- 1561 • have a history of a stroke
- 1562 • have high blood pressure
- 1563 • have or had bleeding problems
- 1564 • have glaucoma (high pressure in the eye)

1565

1566 **Tell your healthcare provider about all the medicines you take**, including prescription and  
1567 non-prescription medicines, vitamins, and herbal supplements. PAXIL and some medicines may  
1568 interact with each other, may not work as well, or may cause serious side effects.

1569 Your healthcare provider or pharmacist can tell you if it is safe to take PAXIL with your other  
1570 medicines. Do not start or stop any medicine while taking PAXIL without talking to your  
1571 healthcare provider first.

1572 If you take PAXIL, you should not take any other medicines that contain paroxetine, including  
1573 PAXIL CR and PEXEVA<sup>®</sup> (paroxetine mesylate).

1574

### 1575 **How should I take PAXIL?**

- 1576 • Take PAXIL exactly as prescribed. Your healthcare provider may need to change the dose of  
1577 PAXIL until it is the right dose for you.
- 1578 • PAXIL may be taken with or without food.
- 1579 • If you are taking PAXIL Oral Suspension, shake the suspension well before use.
- 1580 • If you miss a dose of PAXIL, take the missed dose as soon as you remember. If it is almost  
1581 time for the next dose, skip the missed dose and take your next dose at the regular time. Do  
1582 not take two doses of PAXIL at the same time.
- 1583 • If you take too much PAXIL, call your healthcare provider or poison control center right  
1584 away, or get emergency treatment.
- 1585 • Do not stop taking PAXIL suddenly without talking to your doctor (unless you have  
1586 symptoms of a severe allergic reaction). If you need to stop taking PAXIL, your healthcare  
1587 provider can tell you how to safely stop taking it.

1588

### 1589 **What should I avoid while taking PAXIL?**

1590 PAXIL can cause sleepiness or may affect your ability to make decisions, think clearly, or react  
1591 quickly. You should not drive, operate heavy machinery, or do other dangerous activities until  
1592 you know how PAXIL affects you. Do not drink alcohol while using PAXIL.

1593

### 1594 **What are possible side effects of PAXIL?**

1595 PAXIL may cause serious side effects, including all of those described in the section entitled  
1596 “What is the most important information I should know about PAXIL?”

1597 Common possible side effects in people who take PAXIL include:

- 1598 • nausea
- 1599 • sleepiness
- 1600 • weakness
- 1601 • dizziness
- 1602 • feeling anxious or trouble sleeping
- 1603 • sexual problems
- 1604 • sweating
- 1605 • shaking
- 1606 • not feeling hungry

- 1607 • dry mouth
- 1608 • constipation
- 1609 • infection
- 1610 • yawning

1611 Tell your healthcare provider if you have any side effect that bothers you or that does not go  
1612 away. These are not all the possible side effects of PAXIL. For more information, ask your  
1613 healthcare provider or pharmacist.

1614 **CALL YOUR DOCTOR FOR MEDICAL ADVICE ABOUT SIDE EFFECTS. YOU MAY**  
1615 **REPORT SIDE EFFECTS TO THE FDA AT 1-800-FDA-1088 or 1-800-332-1088.**

1616

#### 1617 **How should I store PAXIL?**

- 1618 • Store PAXIL Tablets at room temperature between 59° and 86°F (15° and 30°C).
- 1619 • Store PAXIL Oral Suspension at or below 77°F (25°C).
- 1620 • Keep PAXIL away from light.
- 1621 • Keep bottle of PAXIL closed tightly.

1622 **Keep PAXIL and all medicines out of the reach of children.**

1623

#### 1624 **General information about PAXIL**

1625 Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.  
1626 Do not use PAXIL for a condition for which it was not prescribed. Do not give PAXIL to other  
1627 people, even if they have the same condition. It may harm them.

1628

1629 This Medication Guide summarizes the most important information about PAXIL. If you would  
1630 like more information, talk with your healthcare provider. You may ask your healthcare provider  
1631 or pharmacist for information about PAXIL that is written for healthcare professionals.

1632

1633 For more information about PAXIL call 1-888-825-5249 or go to [www.us.gsk.com](http://www.us.gsk.com).

1634

#### 1635 **What are the ingredients in PAXIL?**

1636 **Active ingredient:** paroxetine hydrochloride

1637 **Inactive ingredients in tablets:** dibasic calcium phosphate dihydrate, hypromellose, magnesium  
1638 stearate, polyethylene glycols, polysorbate 80, sodium starch glycolate, titanium dioxide, and 1  
1639 or more of the following: D&C Red No. 30 aluminum lake, D&C Yellow No. 10 aluminum lake,  
1640 FD&C Blue No. 2 aluminum lake, FD&C Yellow No. 6 aluminum lake.

1641 **Inactive ingredients in suspension for oral administration:** polacrillin potassium,  
1642 microcrystalline cellulose, propylene glycol, glycerin, sorbitol, methylparaben, propylparaben,  
1643 sodium citrate dihydrate, citric acid anhydrous, sodium saccharin, flavorings, FD&C Yellow  
1644 No. 6 aluminum lake, and simethicone emulsion, USP.



1645  
1646 PAXIL and PAXIL CR are registered trademarks of GlaxoSmithKline. The other brands listed  
1647 are trademarks of their respective owners and are not trademarks of GlaxoSmithKline. The  
1648 makers of these brands are not affiliated with and do not endorse GlaxoSmithKline or its  
1649 products.

1650  
1651 This Medication Guide has been approved by the U.S. Food and Drug Administration.

1652  
1653

1654  GlaxoSmithKline

GlaxoSmithKline  
Research Triangle Park, NC 27709

1655 ©2011, GlaxoSmithKline. All rights reserved.

1656

1657 July 2011

PXL:6MG

1658