

1 PRESCRIBING INFORMATION

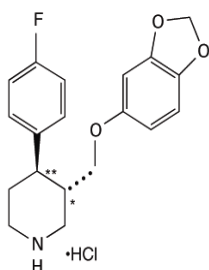
2 **PAXIL<sup>®</sup>**  
3 **(paroxetine hydrochloride)**  
4 **Tablets and Oral Suspension**  
5

6 **Suicidality and Antidepressant Drugs**

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

21 **DESCRIPTION**

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



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

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

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

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

## 41 **CLINICAL PHARMACOLOGY**

42 **Pharmacodynamics:** The efficacy of paroxetine in the treatment of major depressive  
43 disorder, social anxiety disorder, obsessive compulsive disorder (OCD), panic disorder (PD),  
44 generalized anxiety disorder (GAD), and posttraumatic stress disorder (PTSD) is presumed to be  
45 linked to potentiation of serotonergic activity in the central nervous system resulting from  
46 inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT). Studies at clinically  
47 relevant doses in humans have demonstrated that paroxetine blocks the uptake of serotonin into  
48 human platelets. In vitro studies in animals also suggest that paroxetine is a potent and highly  
49 selective inhibitor of neuronal serotonin reuptake and has only very weak effects on  
50 norepinephrine and dopamine neuronal reuptake. In vitro radioligand binding studies indicate  
51 that paroxetine has little affinity for muscarinic,  $\alpha_1$ -,  $\alpha_2$ -, 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 **Absorption and Distribution:** Paroxetine is equally bioavailable from the oral suspension  
66 and tablet.

67 Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the  
68 hydrochloride salt. In a study in which normal male subjects (n = 15) received 30 mg tablets  
69 daily for 30 days, steady-state paroxetine concentrations were achieved by approximately  
70 10 days for most subjects, although it may take substantially longer in an occasional patient. At  
71 steady state, mean values of  $C_{max}$ ,  $T_{max}$ ,  $C_{min}$ , and  $T_{1/2}$  were 61.7 ng/mL (CV 45%), 5.2 hr.  
72 (CV 10%), 30.7 ng/mL (CV 67%), and 21.0 hours (CV 32%), respectively. The steady-state  $C_{max}$

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

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

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

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

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

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

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

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

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

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

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

## 124 **Clinical Trials**

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

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

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

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

<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%

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## 266 **INDICATIONS AND USAGE**

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

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

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

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

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

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

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

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

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



303 the attacks.

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

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

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

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

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

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

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

341 The efficacy of PAXIL in the treatment of GAD was established in two 8-week  
342 placebo-controlled trials in adults with GAD. PAXIL has not been studied in children or

343 adolescents with Generalized Anxiety Disorder (see CLINICAL PHARMACOLOGY—Clinical  
344 Trials).

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

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

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

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

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

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

## 379 **CONTRAINDICATIONS**

380 Concomitant use in patients taking either monoamine oxidase inhibitors (MAOIs), including  
381 linezolid, an antibiotic which is a reversible non-selective MAOI, or thioridazine is

382 contraindicated (see WARNINGS and PRECAUTIONS).

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

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

## 386 **WARNINGS**

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

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

412

413 **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

414

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

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

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

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

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

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

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

444 **Screening Patients for Bipolar Disorder:** A major depressive episode may be the initial

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

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

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

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

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

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

484 **Potential Interaction With Thioridazine:** Thioridazine administration alone produces

485 **prolongation of the QTc interval, which is associated with serious ventricular arrhythmias,**  
486 **such as torsade de pointes–type arrhythmias, and sudden death. This effect appears to be**  
487 **dose related.**

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

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

- 496 • A study based on Swedish national registry data demonstrated that infants exposed to  
497 paroxetine during pregnancy (n = 815) had an increased risk of cardiovascular  
498 malformations (2% risk in paroxetine-exposed infants) compared to the entire registry  
499 population (1% risk), for an odds ratio (OR) of 1.8 (95% confidence interval 1.1 to 2.8).  
500 No increase in the risk of overall congenital malformations was seen in the paroxetine-  
501 exposed infants. The cardiac malformations in the paroxetine-exposed infants were  
502 primarily ventricular septal defects (VSDs) and atrial septal defects (ASDs). Septal  
503 defects range in severity from those that resolve spontaneously to those which require  
504 surgery.
- 505 • A separate retrospective cohort study from the United States (United Healthcare data)  
506 evaluated 5,956 infants of mothers dispensed antidepressants during the first trimester  
507 (n = 815 for paroxetine). This study showed a trend towards an increased risk for  
508 cardiovascular malformations for paroxetine (risk of 1.5%) compared to other  
509 antidepressants (risk of 1%), for an OR of 1.5 (95% confidence interval 0.8 to 2.9). Of  
510 the 12 paroxetine-exposed infants with cardiovascular malformations, 9 had VSDs.  
511 This study also suggested an increased risk of overall major congenital malformations  
512 including cardiovascular defects for paroxetine (4% risk) compared to other (2% risk)  
513 antidepressants (OR 1.8; 95% confidence interval 1.2 to 2.8).
- 514 • Two large case-control studies using separate databases, each with >9,000 birth defect  
515 cases and >4,000 controls, found that maternal use of paroxetine during the first  
516 trimester of pregnancy was associated with a 2- to 3-fold increased risk of right  
517 ventricular outflow tract obstructions. In one study the odds ratio was 2.5 (95%  
518 confidence interval, 1.0 to 6.0, 7 exposed infants) and in the other study the odds ratio  
519 was 3.3 (95% confidence interval, 1.3 to 8.8, 6 exposed infants).

520 Other studies have found varying results as to whether there was an increased risk of overall,  
521 cardiovascular, or specific congenital malformations. A meta-analysis of epidemiological data  
522 over a 16-year period (1992 to 2008) on first trimester paroxetine use in pregnancy and  
523 congenital malformations included the above-noted studies in addition to others (n = 17 studies  
524 that included overall malformations and n = 14 studies that included cardiovascular

525 malformations; n = 20 distinct studies). While subject to limitations, this meta-analysis suggested  
526 an increased occurrence of cardiovascular malformations (prevalence odds ratio [POR] 1.5; 95%  
527 confidence interval 1.2 to 1.9) and overall malformations (POR 1.2; 95% confidence interval 1.1  
528 to 1.4) with paroxetine use during the first trimester. It was not possible in this meta-analysis to  
529 determine the extent to which the observed prevalence of cardiovascular malformations might  
530 have contributed to that of overall malformations, nor was it possible to determine whether any  
531 specific types of cardiovascular malformations might have contributed to the observed  
532 prevalence of all cardiovascular malformations.

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

539 **Animal Findings:** Reproduction studies were performed at doses up to 50 mg/kg/day in rats  
540 and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately  
541 8 (rat) and 2 (rabbit) times the maximum recommended human dose (MRHD) on an mg/m<sup>2</sup>  
542 basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was  
543 an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last  
544 trimester of gestation and continued throughout lactation. This effect occurred at a dose of  
545 1 mg/kg/day or approximately one-sixth of the MRHD on an mg/m<sup>2</sup> basis. The no-effect dose for  
546 rat pup mortality was not determined. The cause of these deaths is not known.

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

557 Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent  
558 pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 – 2 per 1,000 live births in  
559 the general population and is associated with substantial neonatal morbidity and mortality. In a  
560 retrospective case-control study of 377 women whose infants were born with PPHN and 836  
561 women whose infants were born healthy, the risk for developing PPHN was approximately six-  
562 fold higher for infants exposed to SSRIs after the 20<sup>th</sup> week of gestation compared to infants who  
563 had not been exposed to antidepressants during pregnancy. There is currently no corroborative  
564 evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first

565 study that has investigated the potential risk. The study did not include enough cases with  
566 exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk.

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

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

## 575 **PRECAUTIONS**

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

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

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

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

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

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



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

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

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

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

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

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

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

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

643 PAXIL has not been evaluated or used to any appreciable extent in patients with a recent

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

716 **Serotonergic Drugs:** Based on the mechanism of action of SNRIs and SSRIs, including  
717 paroxetine hydrochloride, and the potential for serotonin syndrome, caution is advised when  
718 PAXIL is coadministered with other drugs that may affect the serotonergic neurotransmitter  
719 systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI),  
720 lithium, tramadol, or St. John's Wort (see WARNINGS—Serotonin Syndrome). The concomitant  
721 use of PAXIL with MAOIs (including linezolid) is contraindicated (see  
722 CONTRAINDICATIONS). The concomitant use of PAXIL with other SSRIs, SNRIs or  
723 tryptophan is not recommended (see PRECAUTIONS—Drug Interactions, *Tryptophan*).

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

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

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

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

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

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

752 **Phenytoin:** When a single oral 30-mg dose of PAXIL was administered at phenytoin steady  
753 state (300 mg once daily for 14 days), paroxetine AUC and T<sub>1/2</sub> were reduced (by an average of  
754 50% and 35%, respectively) compared to PAXIL administered alone. In a separate study, when a  
755 single oral 300-mg dose of phenytoin was administered at paroxetine steady state (30 mg once  
756 daily for 14 days), phenytoin AUC was slightly reduced (12% on average) compared to  
757 phenytoin administered alone. Since both drugs exhibit nonlinear pharmacokinetics, the above  
758 studies may not address the case where the 2 drugs are both being chronically dosed. No initial  
759 dosage adjustments are considered necessary when these drugs are coadministered; any  
760 subsequent adjustments should be guided by clinical effect (see ADVERSE REACTIONS—  
761 Postmarketing Reports).

762 **Drugs Metabolized by CYP2D6:** Many drugs, including most drugs effective in the  
763 treatment of major depressive disorder (paroxetine, other SSRIs and many tricyclics), are

764 metabolized by the cytochrome P<sub>450</sub> isozyme CYP2D6. Like other agents that are metabolized by  
765 CYP2D6, paroxetine may significantly inhibit the activity of this isozyme. In most patients  
766 (>90%), this CYP2D6 isozyme is saturated early during dosing with PAXIL. In 1 study, daily  
767 dosing of PAXIL (20 mg once daily) under steady-state conditions increased single dose  
768 desipramine (100 mg) C<sub>max</sub>, AUC, and T<sub>1/2</sub> by an average of approximately 2-, 5-, and 3-fold,  
769 respectively. Concomitant use of paroxetine with risperidone, a CYP2D6 substrate has also been  
770 evaluated. In 1 study, daily dosing of paroxetine 20 mg in patients stabilized on risperidone (4 to  
771 8 mg/day) increased mean plasma concentrations of risperidone approximately 4-fold, decreased  
772 9-hydroxyrisperidone concentrations approximately 10%, and increased concentrations of the  
773 active moiety (the sum of risperidone plus 9-hydroxyrisperidone) approximately 1.4-fold. The  
774 effect of paroxetine on the pharmacokinetics of atomoxetine has been evaluated when both drugs  
775 were at steady state. In healthy volunteers who were extensive metabolizers of CYP2D6,  
776 paroxetine 20 mg daily was given in combination with 20 mg atomoxetine every 12 hours. This  
777 resulted in increases in steady state atomoxetine AUC values that were 6- to 8-fold greater and in  
778 atomoxetine C<sub>max</sub> values that were 3- to 4-fold greater than when atomoxetine was given alone.  
779 Dosage adjustment of atomoxetine may be necessary and it is recommended that atomoxetine be  
780 initiated at a reduced dose when it is given with paroxetine.

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

784 Therefore, coadministration of PAXIL with other drugs that are metabolized by this isozyme,  
785 including certain drugs effective in the treatment of major depressive disorder (e.g., nortriptyline,  
786 amitriptyline, imipramine, desipramine, and fluoxetine), phenothiazines, risperidone, and Type  
787 1C antiarrhythmics (e.g., propafenone, flecainide, and encainide), or that inhibit this enzyme  
788 (e.g., quinidine), should be approached with caution.

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

792 At steady state, when the CYP2D6 pathway is essentially saturated, paroxetine clearance is  
793 governed by alternative P<sub>450</sub> isozymes that, unlike CYP2D6, show no evidence of saturation (see  
794 PRECAUTIONS—*Tricyclic Antidepressants*).

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

804 significance.

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

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

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

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

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

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

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

834 **Procyclidine:** Daily oral dosing of PAXIL (30 mg once daily) increased steady-state AUC<sub>0-</sub>  
835 <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%,  
836 respectively, compared to procyclidine alone at steady state. If anticholinergic effects are seen,  
837 the dose of procyclidine should be reduced.

838 **Beta-Blockers:** In a study where propranolol (80 mg twice daily) was dosed orally for  
839 18 days, the established steady-state plasma concentrations of propranolol were unaltered during  
840 coadministration with PAXIL (30 mg once daily) for the final 10 days. The effects of  
841 propranolol on paroxetine have not been evaluated (see ADVERSE REACTIONS—  
842 Postmarketing Reports).

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

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

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

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

852 **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** Two-year  
853 carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and  
854 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to 2.4 (mouse) and  
855 3.9 (rat) times the MRHD for major depressive disorder, social anxiety disorder, GAD, and  
856 PTSD on a mg/m<sup>2</sup> basis. Because the MRHD for major depressive disorder is slightly less than  
857 that for OCD (50 mg versus 60 mg), the doses used in these carcinogenicity studies were only  
858 2.0 (mouse) and 3.2 (rat) times the MRHD for OCD. There was a significantly greater number of  
859 male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50, and 4/50 for  
860 control, low-, middle-, and high-dose groups, respectively) and a significantly increased linear  
861 trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats  
862 were not affected. Although there was a dose-related increase in the number of tumors in mice,  
863 there was no drug-related increase in the number of mice with tumors. The relevance of these  
864 findings to humans is unknown.

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

869 **Impairment of Fertility:** A reduced pregnancy rate was found in reproduction studies in  
870 rats at a dose of paroxetine of 15 mg/kg/day, which is 2.9 times the MRHD for major depressive  
871 disorder, social anxiety disorder, GAD, and PTSD or 2.4 times the MRHD for OCD on a mg/m<sup>2</sup>  
872 basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity  
873 studies for 2 to 52 weeks. These lesions consisted of vacuolation of epididymal tubular  
874 epithelium at 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with  
875 arrested spermatogenesis at 25 mg/kg/day (9.8 and 4.9 times the MRHD for major depressive  
876 disorder, social anxiety disorder, and GAD; 8.2 and 4.1 times the MRHD for OCD and PD on a  
877 mg/m<sup>2</sup> basis).

878 **Pregnancy:** Pregnancy Category D. See WARNINGS—Usage in Pregnancy: *Teratogenic and*  
879 *Nonteratogenic Effects.*

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

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

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

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

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

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

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

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

## 908 **ADVERSE REACTIONS**

909 **Associated With Discontinuation of Treatment:** Twenty percent (1,199/6,145) of patients  
910 treated with PAXIL in worldwide clinical trials in major depressive disorder and 16.1%  
911 (84/522), 11.8% (64/542), 9.4% (44/469), 10.7% (79/735), and 11.7% (79/676) of patients  
912 treated with PAXIL in worldwide trials in social anxiety disorder, OCD, panic disorder, GAD,  
913 and PTSD, respectively, discontinued treatment due to an adverse event. The most common  
914 events ( $\geq 1\%$ ) associated with discontinuation and considered to be drug related (i.e., those events  
915 associated with dropout at a rate approximately twice or greater for PAXIL compared to placebo)  
916 included the following:

917



	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>1</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>1</sup>	—		1.5%	0%							—	—
Libido Decreased							1.0%	0%			—	—

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

920 1. Incidence corrected for gender.

921

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

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

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

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

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

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

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

958 **Major Depressive Disorder:** Table 2 enumerates adverse events that occurred at an  
959 incidence of 1% or more among paroxetine-treated patients who participated in short-term  
960 (6-week) placebo-controlled trials in which patients were dosed in a range of 20 mg to  
961 50 mg/day. Reported adverse events were classified using a standard COSTART-based  
962 Dictionary terminology.

963

964 **Table 2. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled**  
 965 **Clinical Trials for Major Depressive Disorder<sup>1</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>2</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>3,4</sup>	13%	0%
	Other Male Genital Disorders <sup>3,5</sup>	10%	0%
	Urinary Frequency	3%	1%
	Urination Disorder <sup>6</sup>	3%	0%
	Female Genital Disorders <sup>3,7</sup>	2%	0%

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

- 972 3. Percentage corrected for gender.  
 973 4. Mostly “ejaculatory delay.”  
 974 5. Includes “anorgasmia,” “erectile difficulties,” “delayed ejaculation/orgasm,” and “sexual  
 975 dysfunction,” and “impotence.”  
 976 6. Includes mostly “difficulty with micturition” and “urinary hesitancy.”  
 977 7. Includes mostly “anorgasmia” and “difficulty reaching climax/orgasm.”  
 978

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

980 Table 3 enumerates adverse events that occurred at a frequency of 2% or more among OCD  
 981 patients on PAXIL who participated in placebo-controlled trials of 12-weeks duration in which  
 982 patients were dosed in a range of 20 mg to 60 mg/day or among patients with panic disorder on  
 983 PAXIL who participated in placebo-controlled trials of 10- to 12-weeks duration in which  
 984 patients were dosed in a range of 10 mg to 60 mg/day or among patients with social anxiety  
 985 disorder on PAXIL who participated in placebo-controlled trials of 12-weeks duration in which  
 986 patients were dosed in a range of 20 mg to 50 mg/day.  
 987

988 **Table 3. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled**  
 989 **Clinical Trials for Obsessive Compulsive Disorder, Panic Disorder, and Social Anxiety**  
 990 **Disorder<sup>1</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 Appetite	4%	3%	2%	1%	—	—

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

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

999 2. Percentage corrected for gender.

1000

1001 **Generalized Anxiety Disorder and Posttraumatic Stress Disorder:** Table 4  
 1002 enumerates adverse events that occurred at a frequency of 2% or more among GAD patients on  
 1003 PAXIL who participated in placebo-controlled trials of 8-weeks duration in which patients were  
 1004 dosed in a range of 10 mg/day to 50 mg/day or among PTSD patients on PAXIL who  
 1005 participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a  
 1006 range of 20 mg/day to 50 mg/day.

1007

1008 **Table 4. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled**  
 1009 **Clinical Trials for Generalized Anxiety Disorder and Posttraumatic Stress Disorder<sup>1</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%
Respiratory System	Abnormal Dreams			3%	2%
	Respiratory Disorder	7%	5%	—	—
	Sinusitis	4%	3%	—	—
Special Senses	Yawn	4%	—	2%	<1%
	Abnormal Vision	2%	1%	3%	1%
Urogenital System	Abnormal Ejaculation <sup>2</sup>	25%	2%	13%	2%
	Female Genital Disorder <sup>2</sup>	4%	1%	5%	1%
	Impotence <sup>2</sup>	4%	3%	9%	1%

1010 1. Events reported by at least 2% of GAD and PTSD in patients treated with PAXIL are  
 1011 included, except the following events which had an incidence on placebo  $\geq$  PAXIL [GAD]:  
 1012 Abdominal pain, back pain, trauma, dyspepsia, myalgia, and pharyngitis. [PTSD]: Back pain,  
 1013 headache, anxiety, depression, nervousness, respiratory disorder, pharyngitis, and sinusitis.

1014 2. Percentage corrected for gender.

1015

1016 **Dose Dependency of Adverse Events:** A comparison of adverse event rates in a  
1017 fixed-dose study comparing 10, 20, 30, and 40 mg/day of PAXIL with placebo in the treatment  
1018 of major depressive disorder revealed a clear dose dependency for some of the more common  
1019 adverse events associated with use of PAXIL, as shown in the following table:

1020

1021 **Table 5 . Treatment-Emergent Adverse Experience Incidence in a Dose-Comparison Trial**  
1022 **in the Treatment of Major Depressive Disorder\***

Body System/Preferred Term	Placebo n = 51	PAXIL			
		10 mg n = 102	20 mg n = 104	30 mg n = 101	40 mg n = 102
<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%

1023 \* Rule for including adverse events in table: Incidence at least 5% for 1 of paroxetine groups  
1024 and ≥ twice the placebo incidence for at least 1 paroxetine group.

1025

1026 In a fixed-dose study comparing placebo and 20, 40, and 60 mg of PAXIL in the treatment of  
1027 OCD, there was no clear relationship between adverse events and the dose of PAXIL to which  
1028 patients were assigned. No new adverse events were observed in the group treated with 60 mg of  
1029 PAXIL compared to any of the other treatment groups.

1030 In a fixed-dose study comparing placebo and 10, 20, and 40 mg of PAXIL in the treatment of

1031 panic disorder, there was no clear relationship between adverse events and the dose of PAXIL to  
 1032 which patients were assigned, except for asthenia, dry mouth, anxiety, libido decreased, tremor,  
 1033 and abnormal ejaculation. In flexible-dose studies, no new adverse events were observed in  
 1034 patients receiving 60 mg of PAXIL compared to any of the other treatment groups.

1035 In a fixed-dose study comparing placebo and 20, 40, and 60 mg of PAXIL in the treatment of  
 1036 social anxiety disorder, for most of the adverse events, there was no clear relationship between  
 1037 adverse events and the dose of PAXIL to which patients were assigned.

1038 In a fixed-dose study comparing placebo and 20 and 40 mg of PAXIL in the treatment of  
 1039 generalized anxiety disorder, for most of the adverse events, there was no clear relationship  
 1040 between adverse events and the dose of PAXIL to which patients were assigned, except for the  
 1041 following adverse events: Asthenia, constipation, and abnormal ejaculation.

1042 In a fixed-dose study comparing placebo and 20 and 40 mg of PAXIL in the treatment of  
 1043 posttraumatic stress disorder, for most of the adverse events, there was no clear relationship  
 1044 between adverse events and the dose of PAXIL to which patients were assigned, except for  
 1045 impotence and abnormal ejaculation.

1046 **Adaptation to Certain Adverse Events:** Over a 4- to 6-week period, there was evidence  
 1047 of adaptation to some adverse events with continued therapy (e.g., nausea and dizziness), but less  
 1048 to other effects (e.g., dry mouth, somnolence, and asthenia).

1049 **Male and Female Sexual Dysfunction With SSRIs:** Although changes in sexual desire,  
 1050 sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric  
 1051 disorder, they may also be a consequence of pharmacologic treatment. In particular, some  
 1052 evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward  
 1053 sexual experiences.

1054 Reliable estimates of the incidence and severity of untoward experiences involving sexual  
 1055 desire, performance, and satisfaction are difficult to obtain, however, in part because patients and  
 1056 physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of  
 1057 untoward sexual experience and performance cited in product labeling, are likely to  
 1058 underestimate their actual incidence.

1059 In placebo-controlled clinical trials involving more than 3,200 patients, the ranges for the  
 1060 reported incidence of sexual side effects in males and females with major depressive disorder,  
 1061 OCD, panic disorder, social anxiety disorder, GAD, and PTSD are displayed in Table 6.

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1063

**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%



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

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

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

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

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

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

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

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

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

1104 uninformative and those events where a drug cause was remote. It is important to emphasize that  
1105 although the events reported occurred during treatment with paroxetine, they were not  
1106 necessarily caused by it.

1107 Events are further categorized by body system and listed in order of decreasing frequency  
1108 according to the following definitions: Frequent adverse events are those occurring on 1 or more  
1109 occasions in at least 1/100 patients (only those not already listed in the tabulated results from  
1110 placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in  
1111 1/100 to 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients. Events  
1112 of major clinical importance are also described in the PRECAUTIONS section.

1113 **Body as a Whole:** *Infrequent:* Allergic reaction, chills, face edema, malaise, neck pain;  
1114 *rare:* Adrenergic syndrome, cellulitis, moniliasis, neck rigidity, pelvic pain, peritonitis, sepsis,  
1115 ulcer.

1116 **Cardiovascular System:** *Frequent:* Hypertension, tachycardia; *infrequent:* Bradycardia,  
1117 hematoma, hypotension, migraine, postural hypotension, syncope; *rare:* Angina pectoris,  
1118 arrhythmia nodal, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular  
1119 accident, congestive heart failure, heart block, low cardiac output, myocardial infarct, myocardial  
1120 ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis,  
1121 thrombosis, varicose vein, vascular headache, ventricular extrasystoles.

1122 **Digestive System:** *Infrequent:* Bruxism, colitis, dysphagia, eructation, gastritis,  
1123 gastroenteritis, gingivitis, glossitis, increased salivation, liver function tests abnormal, rectal  
1124 hemorrhage, ulcerative stomatitis; *rare:* Aphthous stomatitis, bloody diarrhea, bulimia,  
1125 cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal  
1126 incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, intestinal obstruction,  
1127 jaundice, melena, mouth ulceration, peptic ulcer, salivary gland enlargement, sialadenitis,  
1128 stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries.

1129 **Endocrine System:** *Rare:* Diabetes mellitus, goiter, hyperthyroidism, hypothyroidism,  
1130 thyroiditis.

1131 **Hemic and Lymphatic Systems:** *Infrequent:* Anemia, leukopenia, lymphadenopathy,  
1132 purpura; *rare:* Abnormal erythrocytes, basophilia, bleeding time increased, eosinophilia,  
1133 hypochromic anemia, iron deficiency anemia, leukocytosis, lymphedema, abnormal  
1134 lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia,  
1135 thrombocythemia, thrombocytopenia.

1136 **Metabolic and Nutritional:** *Frequent:* Weight gain; *infrequent:* Edema, peripheral edema,  
1137 SGOT increased, SGPT increased, thirst, weight loss; *rare:* Alkaline phosphatase increased,  
1138 bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, gamma  
1139 globulins increased, gout, hypercalcemia, hypercholesteremia, hyperglycemia, hyperkalemia,  
1140 hyperphosphatemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, ketosis, lactic  
1141 dehydrogenase increased, non-protein nitrogen (NPN) increased.

1142 **Musculoskeletal System:** *Frequent:* Arthralgia; *infrequent:* Arthritis, arthrosis; *rare:*  
1143 Bursitis, myositis, osteoporosis, generalized spasm, tenosynovitis, tetany.

1144 **Nervous System:** *Frequent:* Emotional lability, vertigo; *infrequent:* Abnormal thinking,  
1145 alcohol abuse, ataxia, dystonia, dyskinesia, euphoria, hallucinations, hostility, hypertonia,  
1146 hypesthesia, hypokinesia, incoordination, lack of emotion, libido increased, manic reaction,  
1147 neurosis, paralysis, paranoid reaction; *rare:* Abnormal gait, akinesia, antisocial reaction, aphasia,  
1148 choreoathetosis, circumoral paresthesias, convulsion, delirium, delusions, diplopia, drug  
1149 dependence, dysarthria, extrapyramidal syndrome, fasciculations, grand mal convulsion,  
1150 hyperalgesia, hysteria, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy,  
1151 nystagmus, peripheral neuritis, psychotic depression, psychosis, reflexes decreased, reflexes  
1152 increased, stupor, torticollis, trismus, withdrawal syndrome.

1153 **Respiratory System:** *Infrequent:* Asthma, bronchitis, dyspnea, epistaxis, hyperventilation,  
1154 pneumonia, respiratory flu; *rare:* Emphysema, hemoptysis, hiccups, lung fibrosis, pulmonary  
1155 edema, sputum increased, stridor, voice alteration.

1156 **Skin and Appendages:** *Frequent:* Pruritus; *infrequent:* Acne, alopecia, contact dermatitis,  
1157 dry skin, ecchymosis, eczema, herpes simplex, photosensitivity, urticaria; *rare:* Angioedema,  
1158 erythema nodosum, erythema multiforme, exfoliative dermatitis, fungal dermatitis, furunculosis;  
1159 herpes zoster, hirsutism, maculopapular rash, seborrhea, skin discoloration, skin hypertrophy,  
1160 skin ulcer, sweating decreased, vesiculobullous rash.

1161 **Special Senses:** *Frequent:* Tinnitus; *infrequent:* Abnormality of accommodation,  
1162 conjunctivitis, ear pain, eye pain, keratoconjunctivitis, mydriasis, otitis media; *rare:* Amblyopia,  
1163 anisocoria, blepharitis, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, eye  
1164 hemorrhage, glaucoma, hyperacusis, night blindness, otitis externa, parosmia, photophobia,  
1165 ptosis, retinal hemorrhage, taste loss, visual field defect.

1166 **Urogenital System:** *Infrequent:* Amenorrhea, breast pain, cystitis, dysuria, hematuria,  
1167 menorrhagia, nocturia, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency,  
1168 vaginitis; *rare:* Abortion, breast atrophy, breast enlargement, endometrial disorder, epididymitis,  
1169 female lactation, fibrocystic breast, kidney calculus, kidney pain, leukorrhea, mastitis,  
1170 metrorrhagia, nephritis, oliguria, salpingitis, urethritis, urinary casts, uterine spasm, urolith,  
1171 vaginal hemorrhage, vaginal moniliasis.

1172 **Postmarketing Reports:** Voluntary reports of adverse events in patients taking PAXIL that  
1173 have been received since market introduction and not listed above that may have no causal  
1174 relationship with the drug include acute pancreatitis, elevated liver function tests (the most  
1175 severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated  
1176 with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism,  
1177 syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and  
1178 galactorrhea, neuroleptic malignant syndrome–like events, serotonin syndrome; extrapyramidal  
1179 symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia,  
1180 oculogyric crisis which has been associated with concomitant use of pimozide; tremor and  
1181 trismus; status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis,  
1182 anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular  
1183 tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, events related

1184 to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and  
1185 agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura). There has been  
1186 a case report of an elevated phenytoin level after 4 weeks of PAXIL and phenytoin  
1187 coadministration. There has been a case report of severe hypotension when PAXIL was added to  
1188 chronic metoprolol treatment.

## 1189 **DRUG ABUSE AND DEPENDENCE**

1190 **Controlled Substance Class:** PAXIL is not a controlled substance.

1191 **Physical and Psychologic Dependence:** PAXIL has not been systematically studied in  
1192 animals or humans for its potential for abuse, tolerance or physical dependence. While the  
1193 clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were  
1194 not systematic and it is not possible to predict on the basis of this limited experience the extent to  
1195 which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently,  
1196 patients should be evaluated carefully for history of drug abuse, and such patients should be  
1197 observed closely for signs of misuse or abuse of PAXIL (e.g., development of tolerance,  
1198 incrementations of dose, drug-seeking behavior).

## 1199 **OVERDOSAGE**

1200 **Human Experience:** Since the introduction of PAXIL in the United States, 342 spontaneous  
1201 cases of deliberate or accidental overdose during paroxetine treatment have been reported  
1202 worldwide (circa 1999). These include overdoses with paroxetine alone and in combination with  
1203 other substances. Of these, 48 cases were fatal and of the fatalities, 17 appeared to involve  
1204 paroxetine alone. Eight fatal cases that documented the amount of paroxetine ingested were  
1205 generally confounded by the ingestion of other drugs or alcohol or the presence of significant  
1206 comorbid conditions. Of 145 non-fatal cases with known outcome, most recovered without  
1207 sequelae. The largest known ingestion involved 2,000 mg of paroxetine (33 times the maximum  
1208 recommended daily dose) in a patient who recovered.

1209 Commonly reported adverse events associated with paroxetine overdose include  
1210 somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other  
1211 notable signs and symptoms observed with overdoses involving paroxetine (alone or with other  
1212 substances) include mydriasis, convulsions (including status epilepticus), ventricular  
1213 dysrhythmias (including torsade de pointes), hypertension, aggressive reactions, syncope,  
1214 hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction  
1215 (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin  
1216 syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

1217 **Overdosage Management:** Treatment should consist of those general measures employed in  
1218 the management of overdose with any drugs effective in the treatment of major depressive  
1219 disorder.

1220 Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital  
1221 signs. General supportive and symptomatic measures are also recommended. Induction of emesis  
1222 is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway

1223 protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic  
1224 patients.

1225 Activated charcoal should be administered. Due to the large volume of distribution of this  
1226 drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of  
1227 benefit. No specific antidotes for paroxetine are known.

1228 A specific caution involves patients who are taking or have recently taken paroxetine who  
1229 might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the  
1230 parent tricyclic and/or an active metabolite may increase the possibility of clinically significant  
1231 sequelae and extend the time needed for close medical observation (see PRECAUTIONS—  
1232 *Drugs Metabolized by Cytochrome CYP2D6*).

1233 In managing overdose, consider the possibility of multiple drug involvement. The physician  
1234 should consider contacting a poison control center for additional information on the treatment of  
1235 any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians'*  
1236 *Desk Reference* (PDR).

## 1237 **DOSAGE AND ADMINISTRATION**

1238 **Major Depressive Disorder: Usual Initial Dosage:** PAXIL should be administered as a  
1239 single daily dose with or without food, usually in the morning. The recommended initial dose is  
1240 20 mg/day. Patients were dosed in a range of 20 to 50 mg/day in the clinical trials demonstrating  
1241 the effectiveness of PAXIL in the treatment of major depressive disorder. As with all drugs  
1242 effective in the treatment of major depressive disorder, the full effect may be delayed. Some  
1243 patients not responding to a 20-mg dose may benefit from dose increases, in 10-mg/day  
1244 increments, up to a maximum of 50 mg/day. Dose changes should occur at intervals of at least  
1245 1 week.

1246 **Maintenance Therapy:** There is no body of evidence available to answer the question of  
1247 how long the patient treated with PAXIL should remain on it. It is generally agreed that acute  
1248 episodes of major depressive disorder require several months or longer of sustained  
1249 pharmacologic therapy. Whether the dose needed to induce remission is identical to the dose  
1250 needed to maintain and/or sustain euthymia is unknown.

1251 Systematic evaluation of the efficacy of PAXIL has shown that efficacy is maintained for  
1252 periods of up to 1 year with doses that averaged about 30 mg.

1253 **Obsessive Compulsive Disorder: Usual Initial Dosage:** PAXIL should be administered  
1254 as a single daily dose with or without food, usually in the morning. The recommended dose of  
1255 PAXIL in the treatment of OCD is 40 mg daily. Patients should be started on 20 mg/day and the  
1256 dose can be increased in 10-mg/day increments. Dose changes should occur at intervals of at  
1257 least 1 week. Patients were dosed in a range of 20 to 60 mg/day in the clinical trials  
1258 demonstrating the effectiveness of PAXIL in the treatment of OCD. The maximum dosage  
1259 should not exceed 60 mg/day.

1260 **Maintenance Therapy:** Long-term maintenance of efficacy was demonstrated in a 6-month  
1261 relapse prevention trial. In this trial, patients with OCD assigned to paroxetine demonstrated a

1262 lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY—  
1263 Clinical Trials). OCD is a chronic condition, and it is reasonable to consider continuation for a  
1264 responding patient. Dosage adjustments should be made to maintain the patient on the lowest  
1265 effective dosage, and patients should be periodically reassessed to determine the need for  
1266 continued treatment.

1267 **Panic Disorder: Usual Initial Dosage:** PAXIL should be administered as a single daily dose  
1268 with or without food, usually in the morning. The target dose of PAXIL in the treatment of panic  
1269 disorder is 40 mg/day. Patients should be started on 10 mg/day. Dose changes should occur in  
1270 10-mg/day increments and at intervals of at least 1 week. Patients were dosed in a range of 10 to  
1271 60 mg/day in the clinical trials demonstrating the effectiveness of PAXIL. The maximum dosage  
1272 should not exceed 60 mg/day.

1273 **Maintenance Therapy:** Long-term maintenance of efficacy was demonstrated in a 3-month  
1274 relapse prevention trial. In this trial, patients with panic disorder assigned to paroxetine  
1275 demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL  
1276 PHARMACOLOGY—Clinical Trials). Panic disorder is a chronic condition, and it is reasonable  
1277 to consider continuation for a responding patient. Dosage adjustments should be made to  
1278 maintain the patient on the lowest effective dosage, and patients should be periodically  
1279 reassessed to determine the need for continued treatment.

1280 **Social Anxiety Disorder: Usual Initial Dosage:** PAXIL should be administered as a single  
1281 daily dose with or without food, usually in the morning. The recommended and initial dosage is  
1282 20 mg/day. In clinical trials the effectiveness of PAXIL was demonstrated in patients dosed in a  
1283 range of 20 to 60 mg/day. While the safety of PAXIL has been evaluated in patients with social  
1284 anxiety disorder at doses up to 60 mg/day, available information does not suggest any additional  
1285 benefit for doses above 20 mg/day (see CLINICAL PHARMACOLOGY—Clinical Trials).

1286 **Maintenance Therapy:** There is no body of evidence available to answer the question of  
1287 how long the patient treated with PAXIL should remain on it. Although the efficacy of PAXIL  
1288 beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials, social anxiety  
1289 disorder is recognized as a chronic condition, and it is reasonable to consider continuation of  
1290 treatment for a responding patient. Dosage adjustments should be made to maintain the patient  
1291 on the lowest effective dosage, and patients should be periodically reassessed to determine the  
1292 need for continued treatment.

1293 **Generalized Anxiety Disorder: Usual Initial Dosage:** PAXIL should be administered as a  
1294 single daily dose with or without food, usually in the morning. In clinical trials the effectiveness  
1295 of PAXIL was demonstrated in patients dosed in a range of 20 to 50 mg/day. The recommended  
1296 starting dosage and the established effective dosage is 20 mg/day. There is not sufficient  
1297 evidence to suggest a greater benefit to doses higher than 20 mg/day. Dose changes should occur  
1298 in 10 mg/day increments and at intervals of at least 1 week.

1299 **Maintenance Therapy:** Systematic evaluation of continuing PAXIL for periods of up to  
1300 24 weeks in patients with Generalized Anxiety Disorder who had responded while taking PAXIL  
1301 during an 8-week acute treatment phase has demonstrated a benefit of such maintenance (see

1302 CLINICAL PHARMACOLOGY—Clinical Trials). Nevertheless, patients should be periodically  
1303 reassessed to determine the need for maintenance treatment.

1304 **Posttraumatic Stress Disorder: Usual Initial Dosage:** PAXIL should be administered as  
1305 a single daily dose with or without food, usually in the morning. The recommended starting  
1306 dosage and the established effective dosage is 20 mg/day. In 1 clinical trial, the effectiveness of  
1307 PAXIL was demonstrated in patients dosed in a range of 20 to 50 mg/day. However, in a fixed  
1308 dose study, there was not sufficient evidence to suggest a greater benefit for a dose of 40 mg/day  
1309 compared to 20 mg/day. Dose changes, if indicated, should occur in 10 mg/day increments and at  
1310 intervals of at least 1 week.

1311 **Maintenance Therapy:** There is no body of evidence available to answer the question of  
1312 how long the patient treated with PAXIL should remain on it. Although the efficacy of PAXIL  
1313 beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials, PTSD is  
1314 recognized as a chronic condition, and it is reasonable to consider continuation of treatment for a  
1315 responding patient. Dosage adjustments should be made to maintain the patient on the lowest  
1316 effective dosage, and patients should be periodically reassessed to determine the need for  
1317 continued treatment.

1318 **Special Populations: Treatment of Pregnant Women During the Third Trimester:**  
1319 Neonates exposed to PAXIL and other SSRIs or SNRIs, late in the third trimester have  
1320 developed complications requiring prolonged hospitalization, respiratory support, and tube  
1321 feeding (see WARNINGS). When treating pregnant women with paroxetine during the third  
1322 trimester, the physician should carefully consider the potential risks and benefits of treatment.  
1323 The physician may consider tapering paroxetine in the third trimester.

1324 **Dosage for Elderly or Debilitated Patients, and Patients With Severe Renal or**  
1325 **Hepatic Impairment:** The recommended initial dose is 10 mg/day for elderly patients,  
1326 debilitated patients, and/or patients with severe renal or hepatic impairment. Increases may be  
1327 made if indicated. Dosage should not exceed 40 mg/day.

1328 **Switching Patients to or From a Monoamine Oxidase Inhibitor:** At least 14 days  
1329 should elapse between discontinuation of an MAOI and initiation of therapy with PAXIL.  
1330 Similarly, at least 14 days should be allowed after stopping PAXIL before starting an MAOI.

1331 **Discontinuation of Treatment With PAXIL:** Symptoms associated with discontinuation of  
1332 PAXIL have been reported (see PRECAUTIONS). Patients should be monitored for these  
1333 symptoms when discontinuing treatment, regardless of the indication for which PAXIL is being  
1334 prescribed. A gradual reduction in the dose rather than abrupt cessation is recommended  
1335 whenever possible. If intolerable symptoms occur following a decrease in the dose or upon  
1336 discontinuation of treatment, then resuming the previously prescribed dose may be considered.  
1337 Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

1338 **NOTE: SHAKE SUSPENSION WELL BEFORE USING.**

## 1339 HOW SUPPLIED

1340 **Tablets:** Film-coated, modified-oval as follows:

1341 10-mg yellow, scored tablets engraved on the front with PAXIL and on the back with 10.  
1342 NDC 0029-3210-13 Bottles of 30  
1343 20-mg pink, scored tablets engraved on the front with PAXIL and on the back with 20.  
1344 NDC 0029-3211-13 Bottles of 30  
1345 NDC 0029-3211-59 Bottles of 90  
1346 NDC 0029-3211-21 SUP 100s (intended for institutional use only)  
1347 30-mg blue tablets engraved on the front with PAXIL and on the back with 30.  
1348 NDC 0029-3212-13 Bottles of 30  
1349 40-mg green tablets engraved on the front with PAXIL and on the back with 40.  
1350 NDC 0029-3213-13 Bottles of 30  
1351 Store tablets between 15° and 30°C (59° and 86°F).  
1352 **Oral Suspension:** Orange-colored, orange-flavored, 10 mg/5 mL, in 250 mL white bottles.  
1353 NDC 0029-3215-48  
1354 Store suspension at or below 25°C (77°F).  
1355 PAXIL is a registered trademark of GlaxoSmithKline.  
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### Medication Guide

1359

### Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal

1360

### Thoughts or Actions

1361

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

1362

1363 Read the Medication Guide that comes with your or your family member’s antidepressant  
1364 medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with  
1365 antidepressant medicines. **Talk to your, or your family member’s, healthcare provider**  
1366 **about:**

1367

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

1368

1369

1370 **What is the most important information I should know about antidepressant medicines,**  
1371 **depression and other serious mental illnesses, and suicidal thoughts or action?**

1372

1373 **1. Antidepressant medicines may increase suicidal thoughts or actions in some children,**  
1374 **teenagers, and young adults within the first few months of treatment.**

1375

1376 **2. Depression and other serious mental illnesses are the most important causes of suicidal**  
1377 **thoughts and actions. Some people may have a particularly high risk of having suicidal**  
1378 **thoughts or actions.** These include people who have (or have a family history of) bipolar  
1379 illness (also called manic-depressive illness) or suicidal thoughts or actions.

1380

1381 **3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a**



1382 **family member?**

- 1383 • Pay close attention to any changes, especially sudden changes, in mood, behaviors,  
1384 thoughts, or feelings. This is very important when an antidepressant medicine is started or  
1385 when the dose is changed.
- 1386 • Call the healthcare provider right away to report new or sudden changes in mood,  
1387 behavior, thoughts, or feelings.
- 1388 • Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare  
1389 provider between visits as needed, especially if you have concerns about symptoms.

1390

1391 **Call a healthcare provider right away if you or your family member has any of the**  
1392 **following symptoms, especially if they are new, worse, or worry you:**

- 1393 • Thoughts about suicide or dying
- 1394 • Attempts to commit suicide
- 1395 • New or worse depression
- 1396 • New or worse anxiety
- 1397 • Feeling very agitated or restless
- 1398 • Panic attacks
- 1399 • Trouble sleeping (insomnia)
- 1400 • New or worse irritability
- 1401 • Acting aggressive, being angry, or violent
- 1402 • Acting on dangerous impulses
- 1403 • An extreme increase in activity and talking (mania)
- 1404 • Other unusual changes in behavior or mood

1405

1406 **What else do I need to know about antidepressant medicines?**

1407

- 1408 • **Never stop an antidepressant medicine without first talking to a healthcare**  
1409 **provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- 1410
- 1411 • **Antidepressants are medicines used to treat depression and other illnesses.** It is  
1412 important to discuss all the risks of treating depression and also the risks of not treating it.  
1413 Patients and their families or other caregivers should discuss all treatment choices with  
1414 the healthcare provider, not just the use of antidepressants.
- 1415
- 1416 • **Antidepressant medicines have other side effects.** Call your doctor for medical advice  
1417 about side effects. You may report side effects to FDA at 1-800-FDA-1088.
- 1418
- 1419 • **Antidepressant medicines can interact with other medicines.** Know all of the  
1420 medicines that you or your family member takes. Keep a list of all medicines to show the  
1421 healthcare provider. Do not start new medicines without first checking with your  
1422 healthcare provider.
- 1423
- 1424 • **Not all antidepressant medicines prescribed for children are FDA approved for use**

1425 **in children.** Talk to your child's healthcare provider for more information.

1426

1427 This Medication Guide has been approved by the U.S. Food and Drug Administration for all  
1428 antidepressants.

1429 January 2008

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1433 Research Triangle Park, NC 27709

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