

April 5, 2006



GlaxoSmithKline

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**Re: NDA 20-031; PAXIL® (paroxetine hydrochloride) Tablets
NDA 20-936; PAXIL CR™ (paroxetine hydrochloride) Controlled-Release Tablets for
Treatment of Depression
NDA 20-982; PAXIL CR™ (paroxetine hydrochloride) Controlled-Release Tablets for
Treatment of Panic Disorder
NDA 20-885; PAXIL® (paroxetine hydrochloride) Capsules
NDA 20-710; PAXIL® (paroxetine hydrochloride) Oral Suspension
General Correspondence: Updated Briefing Document, Clinical, Meeting Request, Statistical
Results from Suicidality Analysis of Adult MDD and non-MDD Paroxetine Clinical Studies**

Dear Dr. Laughren:

Reference is made to our approved New Drug Application for Paxil® (paroxetine hydrochloride) Tablets, NDA 20-031, Paxil® (paroxetine hydrochloride) Oral Suspension, NDA 20-710. Reference is also made to our submission of March 8, 2006, which provided results from the first portion of a comprehensive meta-analysis to evaluate the risk of suicidality in placebo-controlled paroxetine trials in adults with Major Depressive Disorder (MDD).

**Content of Submission and Request for Teleconference with FDA to Discuss
Proposed Labeling Revision and Dear Healthcare Provider Letter**

In this submission, we are providing updated results from the analysis that was provided on March 8, 2006 which incorporates the new analysis results from non-Major Depressive Disorder (non-MDD) paroxetine trials in the adult patient population group which includes the following clinical populations: dysthymic disorder, intermittent brief depression (IBD), bipolar depression, panic disorder, obsessive compulsive disorder (OCD), social anxiety disorder (SAD), posttraumatic stress disorder (PTSD), premenstrual dysphoric disorder (PMDD), alcohol dependent patients (undergoing

**Plaintiff Exhibit
PX-009**

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detoxification), and fibromyalgia. (Attachment 1). The data are being submitted to NDA 20-031 and incorporated by reference into the other referenced NDAs for paroxetine.

We are also providing a draft revised Warnings section of the paroxetine Prescribing Information and a draft Dear Healthcare Professional (DHCP) letter for Agency review and comment and a request for a teleconference the week of April 10 to discuss and agree these items. It is the objective of GSK to secure the Agency's comments and agreement in advance of submission of a Changes Being Effectuated (CBE) labeling supplement and subsequent issuance of a DHCP letter to increase awareness of the labeling change.

Statistical Analysis Methods for Analyzing Suicidality

In addition, we wish to draw the Agency's attention to an observation we made regarding statistical analysis methods for analyzing suicidality data that can lead to divergent results in the analysis results of the common odds ratio and its confidence interval, as well as testing the null hypothesis that the common odds ratio is equal to 1 that may be useful when the Agency conducts its own analysis of combined data of suicidality in antidepressant trials. For the attached GSK analysis, the primary analysis used an exact approach (Mehta et al, 1985) implemented in the statistical software StatXact®. The second approach was to use the Mantel-Haenszel (MH) method, with 0.5 continuity correction (Sutton et al, 2002) applied at the level of the trial. (GSK used this additional approach because it was the same one used by FDA in its analysis of the pediatric datasets.) GSK believes the MH method with continuity correction substantially underestimates the odds ratio for Definitive Suicidal Behavior compared with the exact method, because of the small and disproportionate number of events observed between the two treatment groups and because of the imbalanced randomization in some of the trials. The exact method is not affected by either of these problems, and is designed particularly for sparse datasets such as this. We believe the exact method is the most appropriate statistical method for the assessment of this dataset, and should be used in preference to the MH method with continuity correction.

Summary of Results of Suicidality Analysis in Adults

The general conclusions of the comprehensive analysis revealed the following:

- Young adults, especially those with MDD, may be at increased risk for suicidal behavior during treatment with paroxetine. An analysis of placebo controlled trials of adults with psychiatric disorders showed a higher frequency of suicidal behavior in young adults (prospectively defined as aged 18-24 years) treated with paroxetine compared with placebo, although this difference was not statistically significant.

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- In the older age groups (aged 25-64 years and ≥65 years), no such increase was observed.
- In adults with MDD (all ages), there was a statistically significant increase in the frequency of suicidal behaviour in patients treated with paroxetine compared with placebo. However, the majority of these attempts for paroxetine (8 of 11) were in younger adults aged 18-30 years. These MDD data suggest that the higher frequency observed in the younger adult population across psychiatric disorders may extend beyond the age of 24.
- The analysis revealed substantial evidence of efficacy in all indications. Efficacy of younger adults was comparable to efficacy in older adults.
- It is difficult to conclude a causal relationship between paroxetine and suicidality due to the small incidence and absolute number of events, the retrospective nature of this meta-analysis, and potential for confounding by the fact that the events of interest are a symptom of the psychiatric illnesses themselves.
- Although these most recent findings reveal evidence of a possible increased risk for suicidal behaviour in adult patients with MDD and for younger adults for suicidal behaviour or ideation with MDD and non-MDD disorders, we believe that the overall risk-benefit assessment for the young adult and the adult patient population continues to remain positive.

As stated in our March 8, 2006 submission, GSK concludes that revision of the approved prescribing information are justified to reflect the results from this analysis. Please find attached our draft labeling revisions (Attachment 2) as well as a draft letter to Healthcare Professionals (Attachment 3).

Request for Teleconference

We respectfully request a teleconference with the Agency during the week of April 10th to discuss the findings, review and agree the label revision and secure Agency agreement on the content of the proposed DHCP letter. It is the intent of GSK to subsequently submit revised prescribing information under provisions of a CBE supplement.

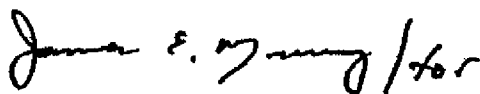
This submission is being provided electronically in accordance with the *Guidance for Industry, Providing Regulatory Submission in Electronic Format – NDAs*, January, 1999. Please see the Guide to FDA Reviewers for detailed information about this electronic submission.

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Should you have any questions regarding this submission or require additional information please contact me by phone at *Redacted* or via secure email at *Redacted*

Sincerely,

Handwritten signature of Barbara E. Arning, M.D.

Barbara E. Arning, M.D.
Senior Director
US Regulatory Affairs, Psychiatry

Trade secret and/or confidential commercial information contained in this submission is exempt from public disclosure to the full extent provided under law.

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UPDATE April 5, 2006

BRIEFING DOCUMENT

Paroxetine Adult Suicidality Analysis: Major Depressive Disorder and Non-Major Depressive Disorder

1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) have been effectively used in the treatment of depressive illness and anxiety disorders since the late 1980s. A possible link between the use of SSRIs and suicidal behavior was first described as a case series in the published literature in 1990 by Teicher et al, who reported that fluoxetine, the first SSRI introduced to the U.S. market, can induce or exacerbate suicidal tendencies. However, subsequent meta-analyses conducted shortly thereafter did not provide evidence supporting this claim, nor did an expert panel convened by FDA in 1991 find any compelling evidence for such an association.

This issue, i.e., whether there is an increased risk of suicidality (suicidal thinking or behavior) associated with SSRI treatment, has been revisited periodically by GlaxoSmithKline (GSK, or legacy company SmithKlineBeecham) with regard to its SSRI paroxetine (Paxil®, Seroxat®, Aropax®, Deroxat®). As was the case for the earlier analyses of fluoxetine and suicidality in adults, these prior investigations of paroxetine's potential association with treatment-emergent suicidality did not produce evidence suggestive of an association in adults. For example, an analysis conducted by GSK in 2002 (submitted to FDA in February 2003) examined the incidence of attempted suicide in all placebo-controlled paroxetine trials in patients with depression. The incidence of suicide attempts in the paroxetine group was 2.1% (66/3192) compared to 1.9% for placebo (38/2047). This difference was not statistically significant ($p=0.61$).

While lack of appropriate treatment is clearly the largest contributor to suicide risk in depressed patients, concerns about SSRI treatment and a possible link to suicidality in some patients have persisted since Teicher first raised this issue. These concerns were heightened further with the recent finding that treatment with SSRIs, including paroxetine, were associated with an increased risk of suicidality relative to placebo in pediatric patients enrolled in controlled clinical trials. Partly as a result of this finding in pediatric patients, a number of regulatory agencies (including the FDA, and the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK) have revisited this issue in adults, particularly in young adults. In May of 2003, an Expert Working Group (EWG) of the Committee on Safety of Medicines was convened in the UK to investigate ongoing public safety concerns with SSRIs, in particular around suicidal behavior and withdrawal reactions/dependence. As part of this review, SSRI manufacturers (including GSK) provided clinical trial data to the EWG in order for this group to conduct its own assessment. The EWG also evaluated available epidemiologic data from the UK General Practice Research Database (GPRD), as well as data from other sources including published literature and spontaneous reports from healthcare professionals.

Upon completion of its analyses, with respect to SSRIs as a class the EWG concluded:

- from the available adult clinical trial data, a modest increase in the risk of suicidal thoughts and self-harm in those taking SSRIs compared with placebo could not be ruled out;
- there was no clear evidence of an increased risk of self-harm and suicidal thoughts in young adults; however, given that individuals mature at different rates and that young adults are at a higher background risk of suicidal behavior than older adults, as a precautionary measure young adults treated with SSRIs should be closely monitored;
- there was insufficient evidence from clinical trial data to conclude any marked difference between members of the SSRI class, or between SSRIs and active comparators, with respect to their influence on suicidal behavior; and,
- evidence from non-experimental GPRD studies indicated that in adults there was no increased risk of suicidal behavior with SSRIs compared with TCAs.

As part of its review, the EWG also conducted a meta-analysis of the adult clinical trials of paroxetine and concluded:

- there was no strong evidence of an increased risk of suicidal events for adult patients with depression exposed to paroxetine compared to placebo, although the point estimates and confidence intervals were consistent with a possible increase in risk.

During the same time period, the MHRA referred paroxetine to European (EU) regulatory authorities for an EU-level review (known as the "Article 31 Referral"). As part of this process, GSK was asked to provide specific analyses of its clinical trial data to evaluate the risk of suicide, suicidal thoughts and self-harm, with particular attention to potential risk factors including age and gender. GSK submitted the 1st set of analyses to the initial Article 31 questions in September 2003 and submitted the 2nd set of analyses in January 2004. Overall, i.e., in all indications studied in placebo-controlled trials in adults, the incidence of possible suicide-related events (i.e., thoughts and behaviors) was similar in the paroxetine and placebo groups (0.8% vs. 0.9%, respectively; OR 0.8 [95% CI 0.6, 1.2]). The findings were similar in the studies conducted specifically in patients with depression (1.7 vs. 1.9%, respectively; OR 0.9 [95% CI 0.6, 1.3]). In the 18-29 years age group, for all indications, the incidence of possibly suicide-related events was greater in the paroxetine group (1.8%) than in the placebo group (1.4%), although this difference was not statistically significant (OR 1.3 [95% CI 0.7, 2.3; p=0.46]).

In April 2004, the EU scientific committee (CHMP) reached their conclusions with respect to paroxetine use in adults, which are summarized as follows:

- The benefit/risk balance for paroxetine remains favorable across all adult indications; and
- There is a possibility of an increased risk of suicidal behavior associated with paroxetine in young adults (18-29 years), although the increased risk was not statistically significant. In the older age groups no such increase was observed. Results from observational studies indicate no increased risk of suicidality in patients who were prescribed paroxetine and likewise, post-

marketing reports indicate low rates of suicidal related behaviors. Clinical trials show similar low rates in placebo and paroxetine treated depressed patients. Rates in patients with other disorders for which paroxetine is indicated are similarly low.

In December 2004 the CHMP reaffirmed these conclusions following consideration of three new epidemiology studies which utilized the UK General Practice Research Database. That same month (Dec 2004) FDA initiated steps to enable its own examination of the relationship between antidepressant use and suicidality in adult patients by requesting all antidepressant manufacturers to provide specified patient-level data from all acute (i.e., ≤ 17 week), double-blind, randomized, placebo-controlled adult studies in major depressive disorder. Potential cases of suicidality were identified via adverse event text string searches, review of serious adverse event (SAE) narratives (including all deaths), and review of the comment fields from the Case Report Forms (CRFs) for all relevant studies. As part of this process, GSK contracted with Columbia University to have independent experts selected by Columbia blindly review each potential case of suicidality and classify the events into suicidal or non-suicidal categories using the same approach used in the pediatric suicidality review conducted by FDA.¹ In May of 2005, FDA expanded its request to also include all acute non-MDD studies (e.g., studies in anxiety disorders such as, OCD, Panic Disorder, Social Anxiety Disorder, etc.). At this time GSK has fully complied with these requests from FDA, i.e., GSK has submitted all required data to FDA (the only exception being the data from one small study conducted in the UK for which the data were not readily available and are currently being retrieved [study #298]).

Recently, GSK decided to conduct its own analyses of the datasets provided to FDA. A briefing document with the results from MDD datasets was submitted to FDA on March 8, 2006. GSK now has completed its analyses of both the MDD-specific and non-MDD specific datasets. This latter group includes the following clinical populations: dysthymic disorder, intermittent brief depression (IBD), bipolar depression, panic disorder, obsessive compulsive disorder (OCD), social anxiety disorder (SAD), posttraumatic stress disorder (PTSD), premenstrual dysphoric disorder (PMDD), alcohol dependent patients (undergoing detoxification), and fibromyalgia. Before conducting this analysis, GSK consulted with external experts to obtain their advice and thoughts as to how to undertake this analysis. In addition, GSK's final statistical analysis plan was submitted on an informational basis to FDA in late December 2005, and to the Dutch MEB (Reference Member State in the EU) in early February 2006.

2. Brief Overview of Methods

The analysis plan developed by GSK for the present analysis of the adult suicidality data (see Appendix I) is based, in part, on methods used previously by FDA during their analysis of pediatric suicidality data. The analysis plan also reflects advice received by external consultants with expertise in suicidality. Because GSK

¹ It should be noted that events were coded by Columbia University in accordance with numerical codes specified by FDA for this review of adult data. These codes differ slightly from those used for the previous FDA review of paediatric studies, owing to the fact that there were no completed suicides in any of the SSRIs pediatric trials.

previously conducted a similar analysis of suicidality data for paroxetine as part of the Article 31 Referral process in 2003, it is important to consider key methodologic differences between the previous and current analysis (see Table 1, below).

Table 1. Key Differences Between Previous Article 31 Analysis and Current Analysis

	Article 31 Analysis	Current Analysis
Events adjudicated by external experts (Columbia University)	No	Yes
Search algorithm for AEs	Algorithm-based search of AE fields	Algorithm-based search of AE fields plus review of CRF comment fields and SAE narratives
Statistical methods	Pooled analysis (crude odds ratios)	Exact method, adjusted by trial (primary method)
Definition of young adults	18-29 yrs	18-24 yrs
Included trials of any duration (ie, included long-term trials where available)	Yes	Yes
Depression analysis – trial groupings	Depressive illnesses together	By indication (eg, MDD, Intermittent Brief Depression, Dysthymia, etc.)
Depression analysis – number of trials	26 depression trials (Dec 1982 through Aug 2001)	19 MDD trials (Dec 1982 to date; ie, through May 2005)
All indications analysis – number of trials	171 studies, including 50 placebo-controlled parallel group trials	57 trials, all placebo-controlled parallel group trials

2.1 Comparison of statistical methods

The analysis of suicidality data has been conducted using two statistical methods for estimating the common odds ratio and its confidence interval, as well as testing the null hypothesis that the common odds ratio is equal to 1. The primary analysis used an exact approach (Mehta et al, 1985) implemented in the statistical software StatXact®. The second approach was to use the Mantel-Haenszel (MH) method, with 0.5 continuity correction (Sutton et al, 2002) applied at the level of the trial. GSK used this additional approach because it was the same one used by FDA in its analysis of the pediatric datasets.

In some cases the results of the analysis of the MDD trials from the two methods diverge substantially. Notably, the odds ratios for Definitive Suicidal Behavior for the MDD population are 6.7 (by the exact method) and 1.6 (by the MH method). The lower odds ratio estimated by the MH method is explained by the addition (under the continuity correction) of 4.5 events to each of the treatment groups which, proportionately, yields a greater increase in the placebo group than in the paroxetine group.

For the endpoint of Rating Scale Emergent Behavior in the MDD population, there is one event on paroxetine (0.03%) and zero events on placebo (0%), but the MH

method estimates the odds ratio to be 0.4 (indicating *lower* risk with paroxetine than placebo). This is a result of the imbalanced randomization in study 009, in which the one event occurred.

With this MDD dataset, GSK believes the MH method with continuity correction substantially underestimates the odds ratio for Definitive Suicidal Behavior compared with the exact method, because of the small and disproportionate number of events observed between the two treatment groups and because of the imbalanced randomization in some of the trials. The exact method is not affected by either of these problems, and is designed particularly for sparse datasets such as this. We believe the exact method is the most appropriate statistical method for the assessment of this dataset, and should be used in preference to the MH method with continuity correction.

3. Clinical Summary

3.1. Major Depressive Disorder

GSK has completed its analysis of paroxetine placebo-controlled clinical trials in patients with Major Depressive Disorder (MDD); see Appendices II - IV. A brief summary of key findings follows:

- On the primary endpoint of definitive suicidal behavior or ideation, there was no statistically significant difference between adults with MDD treated with paroxetine compared to placebo (31/3455 (0.90%) vs. 11/1978 (0.56%); odds ratio = 1.3 (95% CI 0.7, 2.8); $p=0.493$).
- The results provide evidence of an increase in suicide attempts in adults with MDD treated with paroxetine compared to placebo; however, as the absolute number and incidence of events are very small (11/3455 (0.32%) for paroxetine, vs. 1/1978 (0.05%) for placebo; odds ratio = 6.7 (95% CI 1.1, 149.4); $p=0.058$), these data should be interpreted with caution.
- There were proportionally slightly more events (suicidal behavior with or without ideation) in young adults between 18-24 years of age with MDD treated with paroxetine (5/230 (2.17%)) compared to placebo (0/104 (0%)) than in older adults, however these data are not conclusive due to the relatively small sample size of the 18-24 age group and the small number of events. These trends are consistent with findings from previous analyses in pediatrics and adolescents, and while it appears that the risk seen in pediatrics seems to extend beyond age 18, the extent to which this occurs is less clear.
- Although GSK's pre-defined analysis plan did not examine risk in adults aged 25-30 years, it should be noted that review of the 11 cases of definitive suicidal behavior has indicated that five of these patients were aged 25-30 years. Hence, a total of eight of the 11 paroxetine-treated MDD patients with suicidal behavior were aged 18-30 years. This observation suggests that the increased risk of suicidal behavior seen with the overall MDD population was driven primarily by events occurring in the younger adult population.

- 10 of the 11 paroxetine-treated patients with suicidal behavior had experienced improvement in their major depression; and most (9 of 11) of the paroxetine-treated patients had an identified social stressor at the time of the suicide attempt.
- The analysis provided substantial evidence for efficacy in the overall adult MDD population. Paroxetine-treated patients had a significantly greater reduction in HAMD or MADRS from baseline than did placebo. When defining treatment response as a 50% or greater reduction in the primary outcome measure (either the HAMD or MADRS total score), significantly more paroxetine subjects (52.3%) than placebo subjects (37.1%) responded during the clinical trial.
- There was also evidence of efficacy for young adults aged 18-24, although the results indicated some variability in response depending on the depression scale used (ie, HAM-D vs. MADRS). These data are limited, however, due to the small sample size of the 18-24 age group.
- The overall risk-benefit of paroxetine in the treatment of adult patients with MDD remains positive.

The finding of evidence of increased suicide attempts in adults with MDD treated with paroxetine compared to placebo is new, and was not found in GSK's Article 31 analysis or in GSK's prior analyses of suicide attempts. In the Article 31 analysis of self-harm in patients with depressive illness, there were 45 events reported in 3421 patients treated with paroxetine (1.3%), and 33 events in 2117 patients treated with placebo (1.6%), for an odds ratio of 0.84 (95% CI 0.54, 1.32). In contrast, the current analysis of definitive suicidal behavior[†] in patients with MDD revealed 11 events in 3455 patients treated with paroxetine (0.32%), and 1 event in 1978 patients treated with placebo (0.05%); odds ratio 6.7 (95% CI 1.1, 149.4). There are two likely explanations for the difference in results between the prior Article 31 analysis and the current analysis: the datasets included in the analyses, and the methodology used for identifying the relevant events. With respect to the datasets, the current analysis was restricted to a single indication, MDD, consistent with FDA's approach. In terms of the methodology used to identify events, the cases comprising the current analysis were individually reviewed by external experts who were blinded to treatment. As a consequence of the above two factors, 36 events in the paroxetine group and 33 events from the placebo group that were included in the Article 31 analysis of self-harm were not included in the present analysis. The majority of these events (33 paroxetine and 33 placebo) were from two trials investigating intermittent brief depression, and involved patients with a previous history of suicidality. The remaining 3 paroxetine cases were not classified as suicidal behavior by the expert raters. Additionally, there were an additional 2 events identified in the paroxetine group and 1 event in the placebo group that were not identified by the methods used in the Article 31 analysis.

3.2. Non-Major Depressive Disorder

[†] "Definitive suicidal behavior" included events classified as completed suicide, suicide attempt, and preparatory acts toward imminent suicidal behavior. In the results of the current analysis, there were no completed suicides nor events classified as preparatory acts (ie, all events were classified as suicide attempt).

GSK has recently completed its analysis of paroxetine placebo-controlled clinical trials in patients with non-Major Depressive Disorder (non-MDD); see Appendices V - VII. A brief summary of key findings follows:

- In placebo-controlled clinical trials in psychiatric disorders other than MDD, there was no evidence of an increased risk of **suicidal behavior or ideation** (primary endpoint) in patients treated with paroxetine.
 - o "All Indications": 0.93% vs 1.09%; OR 0.9 [95% CI 0.7, 1.3];
p=0.649
 - o "All Depression": 1.77% vs 2.08%; OR 1.1 [95% CI 0.7, 1.7]; p=0.671
 - o "All Non-Depression": 0.32% vs 0.49%; OR 0.7 [95% CI 0.3, 1.3];
p=0.293(Numbers for "All Indications" and "All Depression" include the data from MDD trials).
- There was no evidence of treatment difference in **suicidal behavior alone** (secondary endpoint) in any overall population grouping:
 - o "All Indications": 0.56% vs 0.67%; OR 1.2 [95% CI 0.8, 1.9];
p=0.483
 - o "All Depression": 1.16% vs 1.59%; OR 1.2 [95% CI 0.7, 1.9]; p=0.613
 - o "All Non-Depression": 0.13% vs 0.11%; OR 1.5 [95% CI 0.4, 5.8];
p=0.759
- Although not statistically significant, there were proportionally slightly more events (suicidal behavior with or without ideation) in young adults between 18-24 years of age with psychiatric disorders other than MDD treated with paroxetine (0.99% for paroxetine versus 0.25% for placebo). This finding was consistent across the non-MDD indications.
- Suicidal behavior alone was slightly higher in young adults treated with paroxetine compared with placebo (17/776 [2.19%] versus 5/542 [0.92%]), although this difference was not statistically significant.
- There was evidence of substantial efficacy in the non-MDD population. When defining response as a Clinical Global Impression (CGI) score of "much improved" or "very much improved," significantly more paroxetine subjects (58.8%) responded compared to placebo subjects (39.9%) in the non-depression population.
- As measured by CGI, there were significantly more responders in the paroxetine group versus the placebo group for: panic disorder (68.3% v. 47.4%); OCD (38.3% v. 23.3%); SAD (53.9% v. 31.1%); GAD (64.5% v. 49.4%); PTSD (58.2% v. 39.6%); and PMDD (68.9% v. 42.3%). For each of these populations, there was significant improvement in disease-specific rating scales for paroxetine-treated patients compared to placebo-treated patients.
- Efficacy in young adults was comparable to that in older adults in the non-MDD population.

4. Summary of the Findings and Conclusions

Based on the findings from the MDD and non-MDD datasets, GSK believes that young adults, especially those with MDD, may be at increased risk for suicidal behavior during treatment with paroxetine. An analysis of placebo controlled trials of adults with psychiatric disorders showed a higher frequency of suicidal behavior in young adults (prospectively defined as aged 18-24 years) treated with paroxetine compared with placebo, although this difference was not statistically significant. In the older age groups (aged 25-64 years and ≥ 65 years), no such increase was observed.

In adults with MDD (all ages), there was a statistically significant increase in the frequency of suicidal behaviour in patients treated with paroxetine compared with placebo. However, the majority of these attempts for paroxetine (8 of 11) were in younger adults aged 18-30 years. These MDD data suggest that the higher frequency observed in the younger adult population across psychiatric disorders may extend beyond the age of 24.

The analysis revealed substantial evidence of efficacy in all indications. Efficacy of younger adults was comparable to efficacy in older adults.

It is difficult to conclude a causal relationship between paroxetine and suicidality due to the small incidence and absolute number of events, the retrospective nature of this meta-analysis, and potential for confounding by the fact that the events of interest are a symptom of the psychiatric illnesses themselves. Although these most recent findings reveal evidence of a possible increased risk for suicidal behavior in adult patients with MDD and for younger adults for suicidal behavior or ideation with MDD and non-MDD disorders, we believe that the overall risk-benefit assessment for the young adult and the adult patient population remains positive.

5. Implications for Labeling

Based on these most recent findings in the adult patient dataset GSK concludes that some statements in the approved prescribing information will need to be amended to reflect the results from this analysis.

GSK believes that labeling revisions and/or direct communication with Health Care Professionals (HCPs) should be undertaken.

References:

Teicher MH, Glod C, Cole JO. Emergence of intense suicidal preoccupation during fluoxetine treatment. *Am J Psychiatry* 1990, 147(2):207-10.

Mehta CR, Patel NR, and Gray R. Computing an exact confidence interval for the common odds ratio in several 2x2 contingency tables. *Journal of the American Statistical Association* 1985, Vol 80, no 392.

Sutton AJ, Abrams KR, Jones DR, Sheldon TA, and Song F. Methods for meta-analysis in medical research. *John Wiley & Sons*, NY 2002 page 69.

APPENDIX I: Reporting and Analysis Plan

APPENDIX II: Data Tables: MDD Analysis

APPENDIX III: Figures: MDD Analysis

APPENDIX IV: Narratives MDD: Definitive Suicidal Behavior Events

APPENDIX V: Data Tables: Non-MDD Analysis

APPENDIX VI: Figures: Non-MDD Analysis

APPENDIX VII: Narratives Non-MDD: Definitive Suicidal Behavior Events

PC-L19XX

PRESCRIBING INFORMATION

PAXIL CR®

(paroxetine hydrochloride)

Controlled-Release Tablets

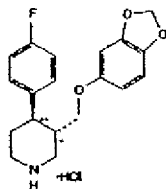
Suicidality in Children and Adolescents

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

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

DESCRIPTION

PAXIL CR (paroxetine hydrochloride) is an orally administered psychotropic drug with a chemical structure unrelated to other selective serotonin reuptake inhibitors or to tricyclic, tetracyclic, or other available antidepressant or antipanic agents. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-*trans*-4*R*-(4'-fluorophenyl)-3*S*-[(3',4'-methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate and has the empirical formula of $C_{19}H_{20}FNO_3 \cdot HCl \cdot 1/2H_2O$. The molecular weight is 374.8 (329.4 as free base). The structural formula of paroxetine hydrochloride is:



PAR004668018

34 Paroxetine hydrochloride is an odorless, off-white powder, having a melting point range of
35 120° to 138°C and a solubility of 5.4 mg/mL in water.

36 Each enteric, film-coated, controlled-release tablet contains paroxetine hydrochloride
37 equivalent to paroxetine as follows: 12.5 mg—yellow, 25 mg—pink, 37.5 mg—blue. One layer of
38 the tablet consists of a degradable barrier layer and the other contains the active material in a
39 hydrophilic matrix.

40 Inactive ingredients consist of hypromellose, polyvinylpyrrolidone, lactose monohydrate,
41 magnesium stearate, colloidal silicon dioxide, glyceryl behenate, methacrylic acid copolymer
42 type C, sodium lauryl sulfate, polysorbate 80, talc, triethyl citrate, and 1 or more of the following
43 colorants: Yellow ferric oxide, red ferric oxide, D&C Red No. 30, D&C Yellow No. 6, D&C
44 Yellow No. 10, FD&C Blue No. 2.

45 CLINICAL PHARMACOLOGY

46 **Pharmacodynamics:** The efficacy of paroxetine in the treatment of major depressive
47 disorder, panic disorder, social anxiety disorder, and premenstrual dysphoric disorder (PMDD) is
48 presumed to be linked to potentiation of serotonergic activity in the central nervous system
49 resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT).
50 Studies at clinically relevant doses in humans have demonstrated that paroxetine blocks the
51 uptake of serotonin into human platelets. In vitro studies in animals also suggest that paroxetine
52 is a potent and highly selective inhibitor of neuronal serotonin reuptake and has only very weak
53 effects on norepinephrine and dopamine neuronal reuptake. In vitro radioligand binding studies
54 indicate that paroxetine has little affinity for muscarinic, α_1 -, α_2 -, beta-adrenergic-,
55 dopamine (D_2)-, 5-HT $_1$ -, 5-HT $_2$ -, and histamine (H_1)-receptors; antagonism of muscarinic,
56 histaminergic, and α_1 -adrenergic receptors has been associated with various anticholinergic,
57 sedative, and cardiovascular effects for other psychotropic drugs.

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

60 **Pharmacokinetics:** Paroxetine hydrochloride is completely absorbed after oral dosing of a
61 solution of the hydrochloride salt. The elimination half-life is approximately 15 to 20 hours after
62 a single dose of PAXIL CR. Paroxetine is extensively metabolized and the metabolites are
63 considered to be inactive. Nonlinearity in pharmacokinetics is observed with increasing doses.
64 Paroxetine metabolism is mediated in part by CYP2D6, and the metabolites are primarily
65 excreted in the urine and to some extent in the feces. Pharmacokinetic behavior of paroxetine has
66 not been evaluated in subjects who are deficient in CYP2D6 (poor metabolizers).

67 **Absorption and Distribution:** Tablets of PAXIL CR contain a degradable polymeric
68 matrix (GEOMATRIX™) designed to control the dissolution rate of paroxetine over a period of
69 approximately 4 to 5 hours. In addition to controlling the rate of drug release in vivo, an enteric
70 coat delays the start of drug release until tablets of PAXIL CR have left the stomach.

71 Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the
72 hydrochloride salt. In a study in which normal male and female subjects (n = 23) received single

oral doses of PAXIL CR at 4 dosage strengths (12.5 mg, 25 mg, 37.5 mg, and 50 mg), paroxetine C_{max} and AUC_{0-24} increased disproportionately with dose (as seen also with immediate-release formulations). Mean C_{max} and AUC_{0-24} values at these doses were 2.0, 5.5, 9.0, and 12.5 ng/mL, and 121, 261, 338, and 540 ng•hr/mL, respectively. T_{max} was observed typically between 6 and 10 hours post-dose, reflecting a reduction in absorption rate compared with immediate-release formulations. The bioavailability of 25 mg PAXIL CR is not affected by food.

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

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

Metabolism and Excretion: The mean elimination half-life of paroxetine was 15 to 20 hours throughout a range of single doses of PAXIL CR (12.5 mg, 25 mg, 37.5 mg, and 50 mg). During repeated administration of PAXIL CR (25 mg once daily), steady state was reached within 2 weeks (i.e., comparable to immediate-release formulations). In a repeat-dose study in which normal male and female subjects ($n = 23$) received PAXIL CR (25 mg daily), mean steady state C_{max} , C_{min} , and AUC_{0-24} values were 30 ng/mL, 20 ng/mL, and 550 ng•hr/mL, respectively.

Based on studies using immediate-release formulations, steady-state drug exposure based on AUC_{0-24} was several-fold greater than would have been predicted from single-dose data. The excess accumulation is a consequence of the fact that 1 of the enzymes that metabolizes paroxetine is readily saturable.

In steady-state dose proportionality studies involving elderly and nonelderly patients, at doses of the immediate-release formulation of 20 mg to 40 mg daily for the elderly and 20 mg to 50 mg daily for the nonelderly, some nonlinearity was observed in both populations, again reflecting a saturable metabolic pathway. In comparison to C_{min} values after 20 mg daily, values after 40 mg daily were only about 2 to 3 times greater than doubled.

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

Approximately 64% of a 30-mg oral solution dose of paroxetine was excreted in the urine with 2% as the parent compound and 62% as metabolites over a 10-day post-dosing period.

About 36% was excreted in the feces (probably via the bile), mostly as metabolites and less than 1% as the parent compound over the 10-day post-dosing period.

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

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

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

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

Clinical Trials

Major Depressive Disorder: The efficacy of PAXIL CR controlled-release tablets as a treatment for major depressive disorder has been established in two 12-week, flexible-dose, placebo-controlled studies of patients with DSM-IV Major Depressive Disorder. One study included patients in the age range 18 to 65 years, and a second study included elderly patients, ranging in age from 60 to 88. In both studies, PAXIL CR was shown to be significantly more effective than placebo in treating major depressive disorder as measured by the following: Hamilton Depression Rating Scale (HDRS), the Hamilton depressed mood item, and the Clinical Global Impression (CGI)—Severity of Illness score.

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

Panic Disorder: The effectiveness of PAXIL CR in the treatment of panic disorder was evaluated in three 10-week, multicenter, flexible-dose studies (Studies 1, 2, and 3) comparing paroxetine controlled-release (12.5 to 75 mg daily) to placebo in adult outpatients who had panic disorder (DSM-IV), with or without agoraphobia. These trials were assessed on the basis of their outcomes on 3 variables: (1) the proportions of patients free of full panic attacks at endpoint; (2) change from baseline to endpoint in the median number of full panic attacks; and (3) change

152 from baseline to endpoint in the median Clinical Global Impression Severity score. For Studies 1
153 and 2, PAXIL CR was consistently superior to placebo on 2 of these 3 variables. Study 3 failed
154 to consistently demonstrate a significant difference between PAXIL CR and placebo on any of
155 these variables.

156 For all 3 studies, the mean dose of PAXIL CR for completers at endpoint was approximately
157 50 mg/day. Subgroup analyses did not indicate that there were any differences in treatment
158 outcomes as a function of age or gender.

159 Long-term maintenance effects of the immediate-release formulation of paroxetine in panic
160 disorder were demonstrated in an extension study. Patients who were responders during a
161 10-week double-blind phase with immediate-release paroxetine and during a 3-month
162 double-blind extension phase were randomized to either immediate-release paroxetine or placebo
163 in a 3-month double-blind relapse prevention phase. Patients randomized to paroxetine were
164 significantly less likely to relapse than comparably treated patients who were randomized to
165 placebo.

166 **Social Anxiety Disorder:** The efficacy of PAXIL CR as a treatment for social anxiety
167 disorder has been established, in part, on the basis of extrapolation from the established
168 effectiveness of the immediate-release formulation of paroxetine. In addition, the effectiveness
169 of PAXIL CR in the treatment of social anxiety disorder was demonstrated in a 12-week,
170 multicenter, double-blind, flexible-dose, placebo-controlled study of adult outpatients with a
171 primary diagnosis of social anxiety disorder (DSM-IV). In the study, the effectiveness of
172 PAXIL CR (12.5 to 37.5 mg daily) compared to placebo was evaluated on the basis of (1)
173 change from baseline in the Liebowitz Social Anxiety Scale (LSAS) total score and (2) the
174 proportion of responders who scored 1 or 2 (very much improved or much improved) on the
175 Clinical Global Impression (CGI) Global Improvement score.

176 PAXIL CR demonstrated statistically significant superiority over placebo on both the LSAS
177 total score and the CGI Improvement responder criterion. For patients who completed the trial,
178 64% of patients treated with PAXIL CR compared to 34.7% of patients treated with placebo
179 were CGI Improvement responders.

180 Subgroup analyses did not indicate that there were any differences in treatment outcomes as a
181 function of gender. Subgroup analyses of studies utilizing the immediate-release formulation of
182 paroxetine generally did not indicate differences in treatment outcomes as a function of age, race,
183 or gender.

184 **Premenstrual Dysphoric Disorder:** The effectiveness of PAXIL CR for the treatment of
185 PMDD utilizing a continuous dosing regimen has been established in 2 placebo-controlled trials.
186 Patients in these trials met DSM-IV criteria for PMDD. In a pool of 1,030 patients, treated with
187 daily doses of PAXIL CR 12.5 or 25 mg/day, or placebo the mean duration of the PMDD
188 symptoms was approximately 11 ± 7 years. Patients on systemic hormonal contraceptives were
189 excluded from these trials. Therefore, the efficacy of PAXIL CR in combination with systemic
190 (including oral) hormonal contraceptives for the continuous daily treatment of PMDD is
191 unknown. In both positive studies, patients (N = 672) were treated with 12.5 mg/day or

192 25 mg/day of PAXIL CR or placebo continuously throughout the menstrual cycle for a period of
193 3 menstrual cycles. The VAS-Total score is a patient-rated instrument that mirrors the diagnostic
194 criteria of PMDD as identified in the DSM-IV, and includes assessments for mood, physical
195 symptoms, and other symptoms. 12.5 mg/day and 25 mg/day of PAXIL CR were significantly
196 more effective than placebo as measured by change from baseline to the endpoint on the luteal
197 phase VAS-Total score.

198 In a third study employing intermittent dosing, patients (N = 366) were treated for the 2 weeks
199 prior to the onset of menses (luteal phase dosing, also known as intermittent dosing) with
200 12.5 mg/day or 25 mg/day of PAXIL CR or placebo for a period of 3 months. 12.5 mg/day and
201 25 mg/day of PAXIL CR, as luteal phase dosing, was significantly more effective than placebo
202 as measured by change from baseline luteal phase VAS total score.

203 There is insufficient information to determine the effect of race or age on outcome in
204 these studies.

205 INDICATIONS AND USAGE

206 **Major Depressive Disorder:** PAXIL CR is indicated for the treatment of major depressive
207 disorder.

208 The efficacy of PAXIL CR in the treatment of a major depressive episode was established in
209 two 12-week controlled trials of outpatients whose diagnoses corresponded to the DSM-IV
210 category of major depressive disorder (see CLINICAL PHARMACOLOGY—Clinical Trials).

211 A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly
212 every day for at least 2 weeks) depressed mood or loss of interest or pleasure in nearly all
213 activities, representing a change from previous functioning, and includes the presence of at least
214 5 of the following 9 symptoms during the same 2-week period: Depressed mood, markedly
215 diminished interest or pleasure in usual activities, significant change in weight and/or appetite,
216 insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of
217 guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt, or suicidal
218 ideation.

219 The antidepressant action of paroxetine in hospitalized depressed patients has not been
220 adequately studied.

221 PAXIL CR has not been systematically evaluated beyond 12 weeks in controlled clinical
222 trials; however, the effectiveness of immediate-release paroxetine hydrochloride in maintaining a
223 response in major depressive disorder for up to 1 year has been demonstrated in a
224 placebo-controlled trial (see CLINICAL PHARMACOLOGY—Clinical Trials). The physician
225 who elects to use PAXIL CR for extended periods should periodically re-evaluate the long-term
226 usefulness of the drug for the individual patient.

227 **Panic Disorder:** PAXIL CR is indicated for the treatment of panic disorder, with or without
228 agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of
229 unexpected panic attacks and associated concern about having additional attacks, worry about

230 the implications or consequences of the attacks, and/or a significant change in behavior related to
231 the attacks.

232 The efficacy of PAXIL CR controlled-release tablets was established in two 10-week trials in
233 panic disorder patients whose diagnoses corresponded to the DSM-IV category of panic disorder
234 (see CLINICAL PHARMACOLOGY—Clinical Trials).

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

243 Long-term maintenance of efficacy with the immediate-release formulation of paroxetine was
244 demonstrated in a 3-month relapse prevention trial. In this trial, patients with panic disorder
245 assigned to immediate-release paroxetine demonstrated a lower relapse rate compared to patients
246 on placebo (see CLINICAL PHARMACOLOGY—Clinical Trials). Nevertheless, the physician
247 who prescribes PAXIL CR for extended periods should periodically re-evaluate the long-term
248 usefulness of the drug for the individual patient.

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

259 The efficacy of PAXIL CR as a treatment for social anxiety disorder has been established, in
260 part, on the basis of extrapolation from the established effectiveness of the immediate-release
261 formulation of paroxetine. In addition, the efficacy of PAXIL CR was established in a 12-week
262 trial, in adult outpatients with social anxiety disorder (DSM-IV). PAXIL CR has not been studied
263 in children or adolescents with social phobia (see CLINICAL PHARMACOLOGY—Clinical
264 Trials).

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

270 **Premenstrual Dysphoric Disorder:** PAXIL CR is indicated for the treatment of PMDD.

271 The efficacy of PAXIL CR in the treatment of PMDD has been established in 3
272 placebo-controlled trials (see CLINICAL PHARMACOLOGY—Clinical Trials).

273 The essential features of PMDD, according to DSM-IV, include markedly depressed mood,
274 anxiety or tension, affective lability, and persistent anger or irritability. Other features include
275 decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite
276 or sleep, and feeling out of control. Physical symptoms associated with PMDD include breast
277 tenderness, headache, joint and muscle pain, bloating, and weight gain. These symptoms occur
278 regularly during the luteal phase and remit within a few days following the onset of menses; the
279 disturbance markedly interferes with work or school or with usual social activities and
280 relationships with others. In making the diagnosis, care should be taken to rule out other cyclical
281 mood disorders that may be exacerbated by treatment with an antidepressant.

282 The effectiveness of PAXIL CR in long-term use, that is, for more than 3 menstrual cycles,
283 has not been systematically evaluated in controlled trials. Therefore, the physician who elects to
284 use PAXIL CR for extended periods should periodically re-evaluate the long-term usefulness of
285 the drug for the individual patient.

286 **CONTRAINDICATIONS**

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

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

290 PAXIL CR is contraindicated in patients with a hypersensitivity to paroxetine or to any of the
291 inactive ingredients in PAXIL CR.

292 **WARNINGS**

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

301 Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and
302 others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of
303 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events
304 representing suicidal behavior or thinking (suicidality) during the first few months of treatment
305 in those receiving antidepressants. The average risk of such events in patients receiving
306 antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk
307 among drugs, but a tendency toward an increase for almost all drugs studied. The risk of
308 suicidality was most consistently observed in the MDD trials, but there were signals of risk

309 arising from some trials in other psychiatric indications (obsessive compulsive disorder and
310 social anxiety disorder) as well. No suicides occurred in any of these trials. It is unknown
311 whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several
312 months. It is also unknown whether the suicidality risk extends to adults.

313 All pediatric patients being treated with antidepressants for any indication should be
314 observed closely for clinical worsening, suicidality, and unusual changes in behavior,
315 especially during the initial few months of a course of drug therapy, or at times of dose
316 changes, either increases or decreases. Such observation would generally include at least
317 weekly face-to-face contact with patients or their family members or caregivers during the
318 first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at
319 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may
320 be appropriate between face-to-face visits.

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

325 Young adults, especially those with MDD, may be at increased risk for suicidal behavior
326 during treatment with paroxetine. An analysis of placebo-controlled trials of adults with
327 psychiatric disorders showed a higher frequency of suicidal behavior in young adults
328 (prospectively defined as aged 18-24 years) treated with paroxetine compared with placebo
329 (17/776 [2.19%] versus 5/542 [0.92%]), although this difference was not statistically significant.
330 In the older age groups (aged 25-64 years and ≥65 years), no such increase was observed. In
331 adults with MDD (all ages), there was a statistically significant increase in the frequency of
332 suicidal behavior in patients treated with paroxetine compared with placebo (11/3455 [0.32%]
333 versus 1/1978 [0.05%]); all of the events were suicide attempts. However, the majority of these
334 attempts for paroxetine (8 of 11) were in younger adults aged 18-30 years. These MDD data
335 suggest that the higher frequency observed in the younger adult population across psychiatric
336 disorders may extend beyond the age of 24.

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

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

348 Consideration should be given to changing the therapeutic regimen, including possibly
349 discontinuing the medication, in patients whose depression is persistently worse, or who are

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350 experiencing emergent suicidality or symptoms that might be precursors to worsening depression
351 or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the
352 patient's presenting symptoms.

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

358 Families and caregivers of pediatric patients being treated with antidepressants for
359 major depressive disorder or other indications, both psychiatric and nonpsychiatric,
360 should be alerted about the need to monitor patients for the emergence of agitation,
361 irritability, unusual changes in behavior, and the other symptoms described above, as well
362 as the emergence of suicidality, and to report such symptoms immediately to health care
363 providers. Such monitoring should include daily observation by families and caregivers.
364 Prescriptions for PAXIL CR should be written for the smallest quantity of tablets consistent with
365 good patient management, in order to reduce the risk of overdose. Families and caregivers of
366 adults being treated for depression should be similarly advised.

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

377 Potential for Interaction With Monoamine Oxidase Inhibitors: In patients receiving
378 another serotonin reuptake inhibitor drug in combination with an MAOI, there have been
379 reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus,
380 autonomic instability with possible rapid fluctuations of vital signs, and mental status
381 changes that include extreme agitation progressing to delirium and coma. These reactions
382 have also been reported in patients who have recently discontinued that drug and have
383 been started on an MAOI. Some cases presented with features resembling neuroleptic
384 malignant syndrome. While there are no human data showing such an interaction with
385 paroxetine hydrochloride, limited animal data on the effects of combined use of paroxetine
386 and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and
387 evoke behavioral excitation. Therefore, it is recommended that PAXIL CR not be used in
388 combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI.
389 At least 2 weeks should be allowed after stopping PAXIL CR before starting an MAOI.

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

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

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

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

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

Animal Findings: Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately

8 (rat) and 2 (rabbit) times the MRHD on an mg/m² basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg/day or approximately one-sixth of the MRHD on an mg/m² basis. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known.

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

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

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

PRECAUTIONS

General: Activation of Mania/Hypomania: During premarketing testing of immediate-release paroxetine hydrochloride, hypomania or mania occurred in approximately 1.0% of paroxetine-treated unipolar patients compared to 1.1% of active-control and 0.3% of placebo-treated unipolar patients. In a subset of patients classified as bipolar, the rate of manic episodes was 2.2% for immediate-release paroxetine and 11.6% for the combined active-control groups. Among 1,627 patients with major depressive disorder, panic disorder, social anxiety disorder, or PMDD treated with PAXIL CR in controlled clinical studies, there were no reports of mania or hypomania. As with all drugs effective in the treatment of major depressive disorder, PAXIL CR should be used cautiously in patients with a history of mania.

Seizures: During premarketing testing of immediate-release paroxetine hydrochloride, seizures occurred in 0.1% of paroxetine-treated patients, a rate similar to that associated with other drugs effective in the treatment of major depressive disorder. Among 1,627 patients who received PAXIL CR in controlled clinical trials in major depressive disorder, panic disorder, social anxiety disorder, or PMDD, 1 patient (0.1%) experienced a seizure. PAXIL CR should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

468 **Discontinuation of Treatment With PAXIL CR:** Adverse events while discontinuing
469 therapy with PAXIL CR were not systematically evaluated in most clinical trials; however, in
470 recent placebo-controlled clinical trials utilizing daily doses of PAXIL CR up to 37.5 mg/day,
471 spontaneously reported adverse events while discontinuing therapy with PAXIL CR were
472 evaluated. Patients receiving 37.5 mg/day underwent an incremental decrease in the daily dose
473 by 12.5 mg/day to a dose of 25 mg/day for 1 week before treatment was stopped. For patients
474 receiving 25 mg/day or 12.5 mg/day, treatment was stopped without an incremental decrease in
475 dose. With this regimen in those studies, the following adverse events were reported for
476 PAXIL CR, at an incidence of 2% or greater for PAXIL CR and were at least twice that reported
477 for placebo: Dizziness, nausea, nervousness, and additional symptoms described by the
478 investigator as associated with tapering or discontinuing PAXIL CR (e.g., emotional lability,
479 headache, agitation, electric shock sensations, fatigue, and sleep disturbances). These events
480 were reported as serious in 0.3% of patients who discontinued therapy with PAXIL CR.

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

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

493 See also PRECAUTIONS—Pediatric Use, for adverse events reported upon discontinuation
494 of treatment with paroxetine in pediatric patients.

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

499 **Hyponatremia:** Several cases of hyponatremia have been reported with immediate-release
500 paroxetine hydrochloride. The hyponatremia appeared to be reversible when paroxetine was
501 discontinued. The majority of these occurrences have been in elderly individuals, some in
502 patients taking diuretics or who were otherwise volume depleted.

503 **Serotonin Syndrome:** The development of a serotonin syndrome may occur in association
504 with treatment with paroxetine, particularly with concomitant use of serotonergic drugs and with
505 drugs which may have impaired metabolism of immediate-release paroxetine hydrochloride.
506 Symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia,
507 myoclonus, shivering, tachycardia, and tremor. The concomitant use of PAXIL CR with

508 serotonin precursors (such as tryptophan) is not recommended (see WARNINGS—Potential for
509 Interaction With Monoamine Oxidase Inhibitors and PRECAUTIONS—Drug Interactions).

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

520 **Use in Patients With Concomitant Illness:** Clinical experience with immediate-release
521 paroxetine hydrochloride in patients with certain concomitant systemic illness is limited. Caution
522 is advisable in using PAXIL CR in patients with diseases or conditions that could affect
523 metabolism or hemodynamic responses.

524 As with other SSRIs, mydriasis has been infrequently reported in premarketing studies with
525 paroxetine hydrochloride. A few cases of acute angle closure glaucoma associated with therapy
526 with immediate-release paroxetine have been reported in the literature. As mydriasis can cause
527 acute angle closure in patients with narrow angle glaucoma, caution should be used when
528 PAXIL CR is prescribed for patients with narrow angle glaucoma.

529 PAXIL CR or the immediate-release formulation has not been evaluated or used to any
530 appreciable extent in patients with a recent history of myocardial infarction or unstable heart
531 disease. Patients with these diagnoses were excluded from clinical studies during premarket
532 testing. Evaluation of electrocardiograms of 682 patients who received immediate-release
533 paroxetine hydrochloride in double-blind, placebo-controlled trials, however, did not indicate
534 that paroxetine is associated with the development of significant ECG abnormalities. Similarly,
535 paroxetine hydrochloride does not cause any clinically important changes in heart rate or blood
536 pressure.

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

540 **Information for Patients:** Prescribers or other health professionals should inform patients,
541 their families, and their caregivers about the benefits and risks associated with treatment with
542 PAXIL CR and should counsel them in its appropriate use. A patient Medication Guide About
543 Using Antidepressants in Children and Teenagers is available for PAXIL CR. The prescriber or
544 health professional should instruct patients, their families, and their caregivers to read the
545 Medication Guide and should assist them in understanding its contents. Patients should be given
546 the opportunity to discuss the contents of the Medication Guide and to obtain answers to any

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

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

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

562 PAXIL CR should not be chewed or crushed, and should be swallowed whole.

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

567 **Interference With Cognitive and Motor Performance:** Any psychoactive drug may
568 impair judgment, thinking, or motor skills. Although in controlled studies immediate-release
569 paroxetine hydrochloride has not been shown to impair psychomotor performance, patients
570 should be cautioned about operating hazardous machinery, including automobiles, until they are
571 reasonably certain that therapy with PAXIL CR does not affect their ability to engage in such
572 activities.

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

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

578 **Alcohol:** Although immediate-release paroxetine hydrochloride has not been shown to
579 increase the impairment of mental and motor skills caused by alcohol, patients should be advised
580 to avoid alcohol while taking PAXIL CR.

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

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

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

587 **Drug Interactions: Tryptophan:** As with other serotonin reuptake inhibitors, an interaction
588 between paroxetine and tryptophan may occur when they are coadministered. Adverse
589 experiences, consisting primarily of headache, nausea, sweating, and dizziness, have been
590 reported when tryptophan was administered to patients taking immediate-release paroxetine.
591 Consequently, concomitant use of PAXIL CR with tryptophan is not recommended (see
592 Serotonin Syndrome).

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

594 **Pimozide:** In a controlled study of healthy volunteers, after immediate-release paroxetine
595 hydrochloride was titrated to 60 mg daily, co-administration of a single dose of 2 mg pimozide
596 was associated with mean increases in pimozide AUC of 151% and C_{max} of 62%, compared to
597 pimozide administered alone. Due to the narrow therapeutic index of pimozide and its known
598 ability to prolong the QT interval, concomitant use of pimozide and PAXIL CR is
599 contraindicated (see CONTRAINDICATIONS).

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

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

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

611 **Triptans:** There have been rare postmarketing reports describing patients with weakness,
612 hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant
613 treatment with a triptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) is
614 clinically warranted, appropriate observation of the patient is advised (see Serotonin Syndrome).

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

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

624 **Phenobarbital:** Phenobarbital induces many cytochrome P₄₅₀ (oxidative) enzymes. When a
625 single oral 30-mg dose of immediate-release paroxetine was administered at phenobarbital
626 steady state (100 mg once daily for 14 days), paroxetine AUC and T_{1/2} were reduced (by an
627 average of 25% and 38%, respectively) compared to paroxetine administered alone. The effect of

paroxetine on phenobarbital pharmacokinetics was not studied. Since paroxetine exhibits nonlinear pharmacokinetics, the results of this study may not address the case where the 2 drugs are both being chronically dosed. No initial dosage adjustment with PAXIL CR is considered necessary when coadministered with phenobarbital; any subsequent adjustment should be guided by clinical effect.

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

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

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

Therefore, coadministration of PAXIL CR with other drugs that are metabolized by this isozyme, including certain drugs effective in the treatment of major depressive disorder (e.g., nortriptyline, amitriptyline, imipramine, desipramine, and fluoxetine), phenothiazines,

risperidone, and Type 1C antiarrhythmics (e.g., propafenone, flecainide, and encainide), or that inhibit this enzyme (e.g., quinidine), should be approached with caution.

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

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

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

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

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

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

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

Lithium: A multiple-dose study with immediate-release paroxetine hydrochloride has shown that there is no pharmacokinetic interaction between paroxetine and lithium carbonate. However, due to the potential for serotonin syndrome, caution is advised when immediate-release paroxetine hydrochloride is coadministered with lithium.

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

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

714 **Procyclidine:** Daily oral dosing of immediate-release paroxetine (30 mg once daily)
715 increased steady-state AUC_{0-24} , C_{max} , and C_{min} values of procyclidine (5 mg oral once daily) by
716 35%, 37%, and 67%, respectively, compared to procyclidine alone at steady state. If
717 anticholinergic effects are seen, the dose of procyclidine should be reduced.

718 **Beta-Blockers:** In a study where propranolol (30 mg twice daily) was dosed orally for
719 18 days, the established steady-state plasma concentrations of propranolol were unaltered during
720 coadministration with immediate-release paroxetine (30 mg once daily) for the final 10 days. The
721 effects of propranolol on paroxetine have not been evaluated (see ADVERSE REACTIONS—
722 Postmarketing Reports).

723 **Theophylline:** Reports of elevated theophylline levels associated with immediate-release
724 paroxetine treatment have been reported. While this interaction has not been formally studied, it
725 is recommended that theophylline levels be monitored when these drugs are concurrently
726 administered.

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

730 **Electroconvulsive Therapy (ECT):** There are no clinical studies of the combined use of
731 ECT and PAXIL CR.

732 **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** Two-year
733 carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and
734 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to approximately 2
735 (mouse) and 3 (rat) times the maximum recommended human dose (MRHD) on a mg/m^2 basis.
736 There was a significantly greater number of male rats in the high-dose group with reticulum cell
737 sarcomas (1/100, 0/50, 0/50, and 4/50 for control, low-, middle-, and high-dose groups,
738 respectively) and a significantly increased linear trend across dose groups for the occurrence of
739 lymphoreticular tumors in male rats. Female rats were not affected. Although there was a
740 dose-related increase in the number of tumors in mice, there was no drug-related increase in the
741 number of mice with tumors. The relevance of these findings to humans is unknown.

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

746 **Impairment of Fertility:** A reduced pregnancy rate was found in reproduction studies in
747 rats at a dose of paroxetine of 15 mg/kg/day, which is approximately twice the MRHD on a

mg/m² basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks. These lesions consisted of vacuolation of epididymal tubular epithelium at 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis at 25 mg/kg/day (approximately 8 and 4 times the MRHD on a mg/m² basis).

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

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

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

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

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

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

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

In a controlled study focusing specifically on elderly patients with major depressive disorder, PAXIL CR was demonstrated to be safe and effective in the treatment of elderly patients (>60 years) with major depressive disorder. (See CLINICAL PHARMACOLOGY—Clinical Trials and ADVERSE REACTIONS—Table 2.)

785 **ADVERSE REACTIONS**

786 The information included under the "Adverse Findings Observed in Short-Term,
787 Placebo-Controlled Trials With PAXIL CR" subsection of ADVERSE REACTIONS is based on
788 data from 11 placebo-controlled clinical trials. Three of these studies were conducted in patients
789 with major depressive disorder, 3 studies were done in patients with panic disorder, 1 study was
790 conducted in patients with social anxiety disorder, and 4 studies were done in female patients
791 with PMDD. Two of the studies in major depressive disorder, which enrolled patients in the age
792 range 18 to 65 years, are pooled. Information from a third study of major depressive disorder,
793 which focused on elderly patients (60 to 88 years), is presented separately as is the information
794 from the panic disorder studies and the information from the PMDD studies. Information on
795 additional adverse events associated with PAXIL CR and the immediate-release formulation of
796 paroxetine hydrochloride is included in a separate subsection (see Other Events).

797 **Adverse Findings Observed in Short-Term, Placebo-Controlled Trials With PAXIL**
798 **CR:**

799 **Adverse Events Associated With Discontinuation of Treatment: Major Depressive**
800 **Disorder:** Ten percent (21/212) of patients treated with PAXIL CR discontinued treatment due
801 to an adverse event in a pool of 2 studies of patients with major depressive disorder. The most
802 common events ($\geq 1\%$) associated with discontinuation and considered to be drug related (i.e.,
803 those events associated with dropout at a rate approximately twice or greater for PAXIL CR
804 compared to placebo) included the following:

	PAXIL CR (n = 212)	Placebo (n = 211)
Nausea	3.7%	0.5%
Asthenia	1.9%	0.5%
Dizziness	1.4%	0.0%
Somnolence	1.4%	0.0%

805

806 In a placebo-controlled study of elderly patients with major depressive disorder, 13% (13/104)
807 of patients treated with PAXIL CR discontinued due to an adverse event. Events meeting the
808 above criteria included the following:

	PAXIL CR (n = 104)	Placebo (n = 109)
Nausea	2.9%	0.0%
Headache	1.9%	0.9%
Depression	1.9%	0.0%
LFT's abnormal	1.9%	0.0%

809

810 **Panic Disorder:** Eleven percent (50/444) of patients treated with PAXIL CR in panic
811 disorder studies discontinued treatment due to an adverse event. Events meeting the above
812 criteria included the following:

	PAXIL CR (n = 444)	Placebo (n = 445)
Nausea	2.9%	0.4%
Insomnia	1.8%	0.0%
Headache	1.4%	0.2%
Asthenia	1.1%	0.0%

813

814 **Social Anxiety Disorder:** Three percent (5/186) of patients treated with PAXIL CR in the
815 social anxiety disorder study discontinued treatment due to an adverse event. Events meeting the
816 above criteria included the following:

	PAXIL CR (n = 186)	Placebo (n = 184)
Nausea	2.2%	0.5%
Headache	1.6%	0.5%
Diarrhea	1.1%	0.5%

817

818 **Premenstrual Dysphoric Disorder:** Spontaneously reported adverse events were
819 monitored in studies of both continuous and intermittent dosing of PAXIL CR in the treatment of
820 PMDD. Generally, there were few differences in the adverse event profiles of the 2 dosing
821 regimens. Thirteen percent (88/681) of patients treated with PAXIL CR in PMDD studies of
822 continuous dosing discontinued treatment due to an adverse event.

823 The most common events ($\geq 1\%$) associated with discontinuation in either group treated with
824 PAXIL CR with an incidence rate that is at least twice that of placebo in PMDD trials that
825 employed a continuous dosing regimen are shown in the following table. This table also shows
826 those events that were dose dependent (indicated with an asterisk) as defined as events having an
827 incidence rate with 25 mg of PAXIL CR that was at least twice that with 12.5 mg of PAXIL CR
828 (as well as the placebo group).

	PAXIL CR 25 mg (n = 348)	PAXIL CR 12.5 mg (n = 333)	Placebo (n = 349)
TOTAL	15%	9.9%	6.3%
Nausea*	6.0%	2.4%	0.9%
Asthenia	4.9%	3.0%	1.4%
Somnolence*	4.3%	1.8%	0.3%
Insomnia	2.3%	1.5%	0.0%
Concentration Impaired*	2.0%	0.6%	0.3%
Dry mouth*	2.0%	0.6%	0.3%
Dizziness*	1.7%	0.6%	0.6%
Decreased Appetite*	1.4%	0.6%	0.0%
Sweating*	1.4%	0.0%	0.3%
Tremor*	1.4%	0.3%	0.0%
Yawn*	1.1%	0.0%	0.0%
Diarrhea	0.9%	1.2%	0.0%

* Events considered to be dose dependent are defined as events having an incidence rate with 25 mg of PAXIL CR that was at least twice that with 12.5 mg of PAXIL CR (as well as the placebo group).

Commonly Observed Adverse Events: Major Depressive Disorder:

The most commonly observed adverse events associated with the use of PAXIL CR in a pool of 2 trials (incidence of 5.0% or greater and incidence for PAXIL CR at least twice that for placebo, derived from Table 1) were: Abnormal ejaculation, abnormal vision, constipation, decreased libido, diarrhea, dizziness, female genital disorders, nausea, somnolence, sweating, trauma, tremor, and yawning.

Using the same criteria, the adverse events associated with the use of PAXIL CR in a study of elderly patients with major depressive disorder were: Abnormal ejaculation, constipation, decreased appetite, dry mouth, impotence, infection, libido decreased, sweating, and tremor.

Panic Disorder: In the pool of panic disorder studies, the adverse events meeting these criteria were: Abnormal ejaculation, somnolence, impotence, libido decreased, tremor, sweating, and female genital disorders (generally anorgasmia or difficulty achieving orgasm).

Social Anxiety Disorder: In the social anxiety disorder study, the adverse events meeting these criteria were: Nausea, asthenia, abnormal ejaculation, sweating, somnolence, impotence, insomnia, and libido decreased.

Premenstrual Dysphoric Disorder: The most commonly observed adverse events associated with the use of PAXIL CR either during continuous dosing or luteal phase dosing (incidence of 5% or greater and incidence for PAXIL CR at least twice that for placebo, derived from Table 5) were: Nausea, asthenia, libido decreased, somnolence, insomnia, female genital disorders, sweating, dizziness, diarrhea, and constipation.

854 In the luteal phase dosing PMDD trial, which employed dosing of 12.5 mg/day or 25 mg/day
855 of PAXIL CR limited to the 2 weeks prior to the onset of menses over 3 consecutive menstrual
856 cycles, adverse events were evaluated during the first 14 days of each off-drug phase. When the
857 3 off-drug phases were combined, the following adverse events were reported at an incidence of
858 2% or greater for PAXIL CR and were at least twice the rate of that reported for placebo:
859 Infection (5.3% versus 2.5%), depression (2.8% versus 0.8%), insomnia (2.4% versus 0.8%),
860 sinusitis (2.4% versus 0%), and asthenia (2.0% versus 0.8%).
861 **Incidence in Controlled Clinical Trials:** Table 1 enumerates adverse events that occurred at
862 an incidence of 1% or more among patients treated with PAXIL CR, aged 18 to 65, who
863 participated in 2 short-term (12-week) placebo-controlled trials in major depressive disorder in
864 which patients were dosed in a range of 25 mg to 62.5 mg/day. Table 2 enumerates adverse
865 events reported at an incidence of 5% or greater among elderly patients (ages 60 to 88) treated
866 with PAXIL CR who participated in a short-term (12-week) placebo-controlled trial in major
867 depressive disorder in which patients were dosed in a range of 12.5 mg to 50 mg/day. Table 3
868 enumerates adverse events reported at an incidence of 1% or greater among patients (19 to 72
869 years) treated with PAXIL CR who participated in short-term (10-week) placebo-controlled trials
870 in panic disorder in which patients were dosed in a range of 12.5 mg to 75 mg/day. Table 4
871 enumerates adverse events reported at an incidence of 1% or greater among adult patients treated
872 with PAXIL CR who participated in a short-term (12-week), double-blind, placebo-controlled
873 trial in social anxiety disorder in which patients were dosed in a range of 12.5 to 37.5 mg/day.
874 Table 5 enumerates adverse events that occurred at an incidence of 1% or more among patients
875 treated with PAXIL CR who participated in three, 12-week, placebo-controlled trials in PMDD
876 in which patients were dosed at 12.5 mg/day or 25 mg/day and in one 12-week
877 placebo-controlled trial in which patients were dosed for 2 weeks prior to the onset of menses
878 (luteal phase dosing) at 12.5 mg/day or 25 mg/day. Reported adverse events were classified
879 using a standard COSTART-based Dictionary terminology.

880 The prescriber should be aware that these figures cannot be used to predict the incidence of
881 side effects in the course of usual medical practice where patient characteristics and other factors
882 differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be
883 compared with figures obtained from other clinical investigations involving different treatments,
884 uses, and investigators. The cited figures, however, do provide the prescribing physician with
885 some basis for estimating the relative contribution of drug and nondrug factors to the side effect
886 incidence rate in the population studied.

887
888 **Table 1. Treatment-Emergent Adverse Events Occurring in $\geq 1\%$ of Patients Treated With**
889 **PAXIL CR in a Pool of 2 Studies in Major Depressive Disorder^{1,2}**

Body System/Adverse Event	% Reporting Event	
	PAXIL CR (n = 212)	Placebo (n = 211)
Body as a Whole		

Body System/Adverse Event	% Reporting Event	
	PAXIL CR (n = 212)	Placebo (n = 211)
Headache	27%	20%
Asthenia	14%	9%
Infection ³	8%	5%
Abdominal Pain	7%	4%
Back Pain	5%	3%
Trauma ⁴	5%	1%
Pain ⁵	3%	1%
Allergic Reaction ⁶	2%	1%
Cardiovascular System		
Tachycardia	1%	0%
Vasodilatation ⁷	2%	0%
Digestive System		
Nausea	22%	10%
Diarrhea	18%	7%
Dry Mouth	15%	8%
Constipation	10%	4%
Flatulence	6%	4%
Decreased Appetite	4%	2%
Vomiting	2%	1%
Nervous System		
Somnolence	22%	8%
Insomnia	17%	9%
Dizziness	14%	4%
Libido Decreased	7%	3%
Tremor	7%	1%
Hypertonia	3%	1%
Paresthesia	3%	1%
Agitation	2%	1%
Confusion	1%	0%
Respiratory System		
Yawn	5%	0%
Rhinitis	4%	1%
Cough Increased	2%	1%
Bronchitis	1%	0%
Skin and Appendages		
Sweating	6%	2%
Photosensitivity	2%	0%
Special Senses		
Abnormal Vision ⁸	5%	1%
Taste Perversion	2%	0%
Urogenital System		
Abnormal Ejaculation ^{9,10}	26%	1%

Body System/Adverse Event	% Reporting Event	
	PAXIL CR (n = 212)	Placebo (n = 211)
Female Genital Disorder ^{9,11}	10%	<1%
Impotence ⁹	5%	3%
Urinary Tract Infection	3%	1%
Menstrual Disorder ⁹	2%	<1%
Vaginitis ⁹	2%	0%

- 890 1. Adverse events for which the PAXIL CR reporting incidence was less
891 than or equal to the placebo incidence are not included. These events are:
892 Abnormal dreams, anxiety, arthralgia, depersonalization, dysmenorrhea,
893 dyspepsia, hyperkinesia, increased appetite, myalgia, nervousness,
894 pharyngitis, purpura, rash, respiratory disorder, sinusitis, urinary
895 frequency, and weight gain.
896 2. <1% means greater than zero and less than 1%.
897 3. Mostly flu.
898 4. A wide variety of injuries with no obvious pattern.
899 5. Pain in a variety of locations with no obvious pattern.
900 6. Most frequently seasonal allergic symptoms.
901 7. Usually flushing.
902 8. Mostly blurred vision.
903 9. Based on the number of males or females.
904 10. Mostly anorgasmia or delayed ejaculation.
905 11. Mostly anorgasmia or delayed orgasm.

906
907 **Table 2. Treatment-Emergent Adverse Events Occurring in ≥5% of**
908 **Patients Treated With PAXIL CR in a Study of Elderly Patients With Major Depressive**
909 **Disorder^{1,2}**

Body System/Adverse Event	% Reporting Event	
	PAXIL CR (n = 104)	Placebo (n = 109)
Body as a Whole		
Headache	17%	13%
Asthenia	15%	14%
Trauma	8%	5%
Infection	6%	2%
Digestive System		
Dry Mouth	18%	7%
Diarrhea	15%	9%
Constipation	13%	5%
Dyspepsia	13%	10%
Decreased Appetite	12%	5%

Body System/Adverse Event	% Reporting Event	
	PAXIL CR (n = 104)	Placebo (n = 109)
Flatulence	8%	7%
Nervous System		
Somnolence	21%	12%
Insomnia	10%	8%
Dizziness	9%	5%
Libido Decreased	8%	<1%
Tremor	7%	0%
Skin and Appendages		
Sweating	10%	<1%
Urogenital System		
Abnormal Ejaculation ^{3,4}	17%	3%
Impotence ³	9%	3%

- 910 1. Adverse events for which the PAXIL CR reporting incidence was less than or
911 equal to the placebo incidence are not included. These events are nausea and
912 respiratory disorder.
913 2. <1% means greater than zero and less than 1%.
914 3. Based on the number of males.
915 4. Mostly anorgasmia or delayed ejaculation.

916
917 Table 3. Treatment-Emergent Adverse Events Occurring in ≥1% of
918 Patients Treated With PAXIL CR in a Pool of 3 Panic Disorder Studies^{1,2}

Body System/Adverse Event	% Reporting Event	
	PAXIL CR (n = 444)	Placebo (n = 445)
Body as a Whole		
Asthenia	15%	10%
Abdominal Pain	6%	4%
Trauma ³	5%	4%
Cardiovascular System		
Vasodilation ⁴	3%	2%
Digestive System		
Nausea	23%	17%
Dry Mouth	13%	9%
Diarrhea	12%	9%
Constipation	9%	6%
Decreased Appetite	8%	6%
Metabolic/Nutritional Disorders		
Weight Loss	1%	0%
Musculoskeletal System		
Myalgia	5%	3%
Nervous System		

Body System/Adverse Event	% Reporting Event	
	PAXIL CR (n = 444)	Placebo (n = 445)
Insomnia	20%	11%
Somnolence	20%	9%
Libido Decreased	9%	4%
Nervousness	8%	7%
Tremor	8%	2%
Anxiety	5%	4%
Agitation	3%	2%
Hypertonia ⁵	2%	<1%
Myoclonus	2%	<1%
Respiratory System		
Sinusitis	8%	5%
Yawn	3%	0%
Skin and Appendages		
Sweating	7%	2%
Special Senses		
Abnormal Vision ⁶	3%	<1%
Urogenital System		
Abnormal Ejaculation ^{7,8}	27%	3%
Impotence ⁷	10%	1%
Female Genital Disorders ^{9,10}	7%	1%
Urinary Frequency	2%	<1%
Urination Impaired	2%	<1%
Vaginitis ⁹	1%	<1%

- 919 1. Adverse events for which the reporting rate for PAXIL CR was less than or equal
920 to the placebo rate are not included. These events are: Abnormal dreams, allergic
921 reaction, back pain, bronchitis, chest pain, concentration impaired, confusion,
922 cough increased, depression, dizziness, dysmenorrhea, dyspepsia, fever,
923 flatulence, headache, increased appetite, infection, menstrual disorder, migraine,
924 pain, paresthesia, pharyngitis, respiratory disorder, rhinitis, tachycardia, taste
925 perversion, thinking abnormal, urinary tract infection, and vomiting.
- 926 2. <1% means greater than zero and less than 1%.
- 927 3. Various physical injuries.
- 928 4. Mostly flushing.
- 929 5. Mostly muscle tightness or stiffness.
- 930 6. Mostly blurred vision.
- 931 7. Based on the number of male patients.
- 932 8. Mostly anorgasmia or delayed ejaculation.
- 933 9. Based on the number of female patients.
- 934 10. Mostly anorgasmia or difficulty achieving orgasm.
- 935

936 Table 4. Treatment-Emergent Adverse Effects Occurring in $\geq 1\%$ of Patients Treated With
937 PAXIL CR in a Social Anxiety Disorder Study^{1,2}

Body System/Adverse Event	% Reporting Event	
	PAXIL CR (n = 186)	Placebo (n = 184)
Body as a Whole		
Headache	23%	17%
Asthenia	18%	7%
Abdominal Pain	5%	4%
Back Pain	4%	1%
Trauma ³	3%	<1%
Allergic Reaction ⁴	2%	<1%
Chest Pain	1%	<1%
Cardiovascular System		
Hypertension	2%	0%
Migraine	2%	1%
Tachycardia	2%	1%
Digestive System		
Nausea	22%	6%
Diarrhea	9%	8%
Constipation	5%	2%
Dry Mouth	3%	2%
Dyspepsia	2%	<1%
Decreased Appetite	1%	<1%
Tooth Disorder	1%	0%
Metabolic/Nutritional Disorders		
Weight Gain	3%	1%
Weight Loss	1%	0%
Nervous System		
Insomnia	9%	4%
Somnolence	9%	4%
Libido Decreased	8%	1%
Dizziness	7%	4%
Tremor	4%	2%
Anxiety	2%	1%
Concentration Impaired	2%	0%
Depression	2%	1%
Myoclonus	1%	<1%
Paresthesia	1%	<1%
Respiratory System		
Yawn	2%	0%
Skin and Appendages		
Sweating	14%	3%
Eczema	1%	0%

Body System/Adverse Event	% Reporting Event	
	PAXIL CR (n = 186)	Placebo (n = 184)
Special Senses		
Abnormal Vision ⁵	2%	0%
Abnormality of Accommodation	2%	0%
Urogenital System		
Abnormal Ejaculation ^{6,7}	15%	1%
Impotence ⁶	9%	0%
Female Genital Disorders ^{8,9}	3%	0%

- 938 1. Adverse events for which the reporting rate for PAXIL CR was less than or equal to the
939 placebo rate are not included. These events are: Dysmenorrhea, flatulence, gastroenteritis,
940 hypertonía, infection, pain, pharyngitis, rash, respiratory disorder, rhinitis, and vomiting.
941 2. <1% means greater than zero and less than 1%.
942 3. Various physical injuries.
943 4. Most frequently seasonal allergic symptoms.
944 5. Mostly blurred vision.
945 6. Based on the number of male patients.
946 7. Mostly anorgasmia or delayed ejaculation.
947 8. Based on the number of female patients.
948 9. Mostly anorgasmia or difficulty achieving orgasm.
949

950 Table 5. Treatment-Emergent Adverse Events Occurring in $\geq 1\%$ of Patients Treated With
 951 PAXIL CR in a Pool of 3 Premenstrual Dysphoric Disorder Studies with Continuous
 952 Dosing or in 1 Premenstrual Dysphoric Disorder Study with Luteal Phase Dosing^{1,2,3}

Body System/Adverse Event	% Reporting Event			
	Continuous Dosing		Luteal Phase Dosing	
	PAXIL CR (n = 681)	Placebo (n = 349)	PAXIL CR (n = 246)	Placebo (n = 120)
Body as a Whole				
Asthenia	17%	6%	15%	4%
Headache	15%	12%	-	-
Infection	6%	4%	-	-
Abdominal pain	-	-	3%	0%
Cardiovascular System				
Migraine	1%	<1%	-	-
Digestive System				
Nausea	17%	7%	18%	2%
Diarrhea	6%	2%	6%	0%
Constipation	5%	1%	2%	<1%
Dry Mouth	4%	2%	2%	<1%
Increased Appetite	3%	<1%	-	-
Decreased Appetite	2%	<1%	2%	0%
Dyspepsia	2%	1%	2%	2%
Gingivitis	-	-	1%	0%
Metabolic and Nutritional Disorders				
Generalized Edema	-	-	1%	<1%
Weight Gain	-	-	1%	<1%
Musculoskeletal System				
Arthralgia	2%	1%	-	-
Nervous System				
Libido Decreased	12%	5%	9%	6%
Somnolence	9%	2%	3%	<1%
Insomnia	8%	2%	7%	3%
Dizziness	7%	3%	6%	3%
Tremor	4%	<1%	5%	0%
Concentration Impaired	3%	<1%	1%	0%
Nervousness	2%	<1%	3%	2%
Anxiety	2%	1%	-	-
Lack of Emotion	2%	<1%	-	-
Depression	-	-	2%	<1%
Vertigo	-	-	2%	<1%
Abnormal Dreams	1%	<1%	-	-
Amnesia	-	-	1%	0%

Body System/Adverse Event	% Reporting Event			
	Continuous Dosing		Luteal Phase Dosing	
	PAXIL CR (n = 681)	Placebo (n = 349)	PAXIL CR (n = 246)	Placebo (n = 120)
Respiratory System				
Sinusitis	-	-	4%	2%
Yawn	2%	<1%	-	-
Bronchitis	-	-	2%	0%
Cough Increased	1%	<1%	-	-
Skin and Appendages				
Sweating	7%	<1%	6%	<1%
Special Senses				
Abnormal Vision	-	-	1%	0%
Urogenital System				
Female Genital Disorders ⁴	8%	1%	2%	0%
Menorrhagia	1%	<1%	-	-
Vaginal Moniliasis	1%	<1%	-	-
Menstrual Disorder	-	-	1%	0%

- 953 1. Adverse events for which the reporting rate of PAXIL CR was less than or equal to the
954 placebo rate are not included. These events for continuous dosing are: Abdominal pain, back
955 pain, pain, trauma, weight gain, myalgia, pharyngitis, respiratory disorder, rhinitis, sinusitis,
956 pruritis, dysmenorrhea, menstrual disorder, urinary tract infection, and vomiting. The events for
957 luteal phase dosing are: Allergic reaction, back pain, headache, infection, pain, trauma, myalgia,
958 anxiety, pharyngitis, respiratory disorder, cystitis, and dysmenorrhea.
- 959 2. <1% means greater than zero and less than 1%.
- 960 3. The luteal phase and continuous dosing PMDD trials were not designed for making direct
961 comparisons between the 2 dosing regimens. Therefore, a comparison between the 2 dosing
962 regimens of the PMDD trials of incidence rates shown in Table 5 should be avoided.
- 963 4. Mostly anorgasmia or difficulty achieving orgasm.

964

965 **Dose Dependency of Adverse Events:** The following table shows results in PMDD
966 trials of common adverse events, defined as events with an incidence of $\geq 1\%$ with 25 mg of
967 PAXIL CR that was at least twice that with 12.5 mg of PAXIL CR and with placebo.
968

Incidence of Common Adverse Events in Placebo, 12.5 mg and 25 mg of PAXIL CR in a Pool of 3 Fixed-Dose PMDD Trials

Common Adverse Event	PAXIL CR 25 mg (n = 348)	PAXIL CR 12.5 mg (n = 333)	Placebo (n = 349)
Sweating	8.9%	4.2%	0.9%
Tremor	6.0%	1.5%	0.3%
Concentration Impaired	4.3%	1.5%	0.6%
Yawn	3.2%	0.9%	0.3%
Paresthesia	1.4%	0.3%	0.3%
Hyperkinesia	1.1%	0.3%	0.0%
Vaginitis	1.1%	0.3%	0.3%

A comparison of adverse event rates in a fixed-dose study comparing immediate-release paroxetine with placebo in the treatment of major depressive disorder revealed a clear dose dependency for some of the more common adverse events associated with the use of immediate-release paroxetine.

Male and Female Sexual Dysfunction With SSRIs: Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences.

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

The percentage of patients reporting symptoms of sexual dysfunction in the pool of 2 placebo-controlled trials in nonelderly patients with major depressive disorder, in the pool of 3 placebo-controlled trials in patients with panic disorder, in the placebo-controlled trial in patients with social anxiety disorder, and in the intermittent dosing and the pool of 3 placebo-controlled continuous dosing trials in female patients with PMDD are as follows:

	Major Depressive Disorder		Panic Disorder		Social Anxiety Disorder		PMDD Continuous Dosing		PMDD Luteal Phase Dosing	
	PAXIL CR	Placebo	PAXIL CR	Placebo	PAXIL CR	Placebo	PAXIL CR	Placebo	PAXIL CR	Placebo
n (males)	78	78	162	194	88	97	n/a	n/a	n/a	n/a
Decreased Libido	10%	5%	9%	6%	13%	1%	n/a	n/a	n/a	n/a
Ejaculatory Disturbance	26%	1%	27%	3%	15%	1%	n/a	n/a	n/a	n/a
Impotence	5%	3%	10%	1%	9%	0%	n/a	n/a	n/a	n/a
n (females)	134	133	282	251	98	87	681	349	246	120
Decreased Libido	4%	2%	8%	2%	4%	1%	12%	5%	9%	6%
Orgasmic Disturbance	10%	<1%	7%	1%	3%	0%	8%	1%	2%	0%

989

990 There are no adequate, controlled studies examining sexual dysfunction with paroxetine
991 treatment.

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

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

996 **Weight and Vital Sign Changes:** Significant weight loss may be an undesirable result of
997 treatment with paroxetine for some patients but, on average, patients in controlled trials with
998 PAXIL CR or the immediate-release formulation, had minimal weight loss (about 1 pound). No
999 significant changes in vital signs (systolic and diastolic blood pressure, pulse, and temperature)
1000 were observed in patients treated with PAXIL CR, or immediate-release paroxetine
1001 hydrochloride, in controlled clinical trials.

1002 **ECG Changes:** In an analysis of ECGs obtained in 682 patients treated with
1003 immediate-release paroxetine and 415 patients treated with placebo in controlled clinical trials,
1004 no clinically significant changes were seen in the ECGs of either group.

1005 **Liver Function Tests:** In a pool of 2 placebo-controlled clinical trials, patients treated with
1006 PAXIL CR or placebo exhibited abnormal values on liver function tests at comparable rates. In
1007 particular, the controlled-release paroxetine-versus-placebo comparisons for alkaline
1008 phosphatase, SGOT, SGPT, and bilirubin revealed no differences in the percentage of patients
1009 with marked abnormalities.

1010 In a study of elderly patients with major depressive disorder, 3 of 104 patients treated with
1011 PAXIL CR and none of 109 placebo patients experienced liver transaminase elevations of
1012 potential clinical concern.

1013 Two of the patients treated with PAXIL CR dropped out of the study due to abnormal liver
1014 function tests; the third patient experienced normalization of transaminase levels with continued
1015 treatment. Also, in the pool of 3 studies of patients with panic disorder, 4 of 444 patients treated
1016 with PAXIL CR and none of 445 placebo patients experienced liver transaminase elevations of
1017 potential clinical concern. Elevations in all 4 patients decreased substantially after
1018 discontinuation of PAXIL CR. The clinical significance of these findings is unknown.

1019 In placebo-controlled clinical trials with the immediate-release formulation of paroxetine,
1020 patients exhibited abnormal values on liver function tests at no greater rate than that seen in
1021 placebo-treated patients.

1022 **Hallucinations:** In pooled clinical trials of immediate-release paroxetine hydrochloride,
1023 hallucinations were observed in 22 of 9089 patients receiving drug and in 4 of 3187 patients
1024 receiving placebo.

1025 **Other Events Observed During the Clinical Development of Paroxetine:** The
1026 following adverse events were reported during the clinical development of PAXIL CR and/or the
1027 clinical development of the immediate-release formulation of paroxetine.

1028 Adverse events for which frequencies are provided below occurred in clinical trials with the
1029 controlled-release formulation of paroxetine. During its premarketing assessment in major
1030 depressive disorder, panic disorder, social anxiety disorder, and PMDD multiple doses of
1031 PAXIL CR were administered to 1,627 patients in phase 3 double-blind, controlled, outpatient
1032 studies. Untoward events associated with this exposure were recorded by clinical investigators
1033 using terminology of their own choosing. Consequently, it is not possible to provide a
1034 meaningful estimate of the proportion of individuals experiencing adverse events without first
1035 grouping similar types of untoward events into a smaller number of standardized event
1036 categories.

1037 In the tabulations that follow, reported adverse events were classified using a
1038 COSTART-based dictionary. The frequencies presented, therefore, represent the proportion of
1039 the 1,627 patients exposed to PAXIL CR who experienced an event of the type cited on at least 1
1040 occasion while receiving PAXIL CR. All reported events are included except those already listed
1041 in Tables 1 through 5 and those events where a drug cause was remote. If the COSTART term
1042 for an event was so general as to be uninformative, it was deleted or, when possible, replaced
1043 with a more informative term. It is important to emphasize that although the events reported
1044 occurred during treatment with paroxetine, they were not necessarily caused by it.

1045 Events are further categorized by body system and listed in order of decreasing frequency
1046 according to the following definitions: Frequent adverse events are those occurring on 1 or more
1047 occasions in at least 1/100 patients (only those not already listed in the tabulated results from
1048 placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in
1049 1/100 to 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients.

1050 Adverse events for which frequencies are not provided occurred during the premarketing
1051 assessment of immediate-release paroxetine in phase 2 and 3 studies of major depressive
1052 disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized

1053 anxiety disorder, and posttraumatic stress disorder. The conditions and duration of exposure to
1054 immediate-release paroxetine varied greatly and included (in overlapping categories) open and
1055 double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and
1056 fixed-dose and titration studies. Only those events not previously listed for controlled-release
1057 paroxetine are included. The extent to which these events may be associated with PAXIL CR is
1058 unknown.

1059 Events are listed alphabetically within the respective body system. Events of major clinical
1060 importance are also described in the PRECAUTIONS section.

1061 **Body as a Whole:** Infrequent were chills, face edema, fever, flu syndrome, malaise; rare
1062 were abscess, anaphylactoid reaction, anticholinergic syndrome, hypothermia; also observed
1063 were adrenergic syndrome, neck rigidity, sepsis.

1064 **Cardiovascular System:** Infrequent were angina pectoris, bradycardia, hematoma,
1065 hypertension, hypotension, palpitation, postural hypotension, supraventricular tachycardia,
1066 syncope; rare were bundle branch block; also observed were arrhythmia nodal, atrial fibrillation,
1067 cerebrovascular accident, congestive heart failure, low cardiac output, myocardial infarct,
1068 myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles,
1069 thrombophlebitis, thrombosis, vascular headache, ventricular extrasystoles.

1070 **Digestive System:** Infrequent were bruxism, dysphagia, eructation, gastritis,
1071 gastroenteritis, gastroesophageal reflux, gingivitis, hemorrhoids, liver function test abnormal,
1072 melena, pancreatitis, rectal hemorrhage, toothache, ulcerative stomatitis; rare were colitis,
1073 glossitis, gum hyperplasia, hepatosplenomegaly, increased salivation, intestinal obstruction,
1074 peptic ulcer, stomach ulcer, throat tightness; also observed were aphthous stomatitis, bloody
1075 diarrhea, bulimia, cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions,
1076 fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, jaundice, mouth
1077 ulceration, salivary gland enlargement, sialadenitis, stomatitis, tongue discoloration, tongue
1078 edema.

1079 **Endocrine System:** Infrequent were ovarian cyst, testes pain; rare were diabetes mellitus,
1080 hyperthyroidism; also observed were goiter, hypothyroidism, thyroiditis.

1081 **Hemic and Lymphatic System:** Infrequent were anemia, eosinophilia, hypochromic
1082 anemia, leukocytosis, leukopenia, lymphadenopathy, purpura; rare were thrombocytopenia; also
1083 observed were anisocytosis, basophilia, bleeding time increased, lymphedema, lymphocytosis,
1084 lymphopenia, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia.

1085 **Metabolic and Nutritional Disorders:** Infrequent were generalized edema,
1086 hyperglycemia, hypokalemia, peripheral edema, SGOT increased, SGPT increased, thirst; rare
1087 were bilirubinemia, dehydration, hyperkalemia, obesity; also observed were alkaline phosphatase
1088 increased, BUN increased, creatinine phosphokinase increased, gamma globulins increased,
1089 gout, hypercalcaemia, hypercholesteremia, hyperphosphatemia, hypocalcemia, hypoglycemia,
1090 hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased.

1091 **Musculoskeletal System:** Infrequent were arthritis, bursitis, tendonitis; rare were
1092 myasthenia, myopathy, myositis; also observed were generalized spasm, osteoporosis,
1093 tenosynovitis, tetany.

1094 **Nervous System:** Frequent were depression; infrequent were amnesia, convulsion,
1095 depersonalization, dystonia, emotional lability, hallucinations, hyperkinesia, hypesthesia,
1096 hypokinesia, incoordination, libido increased, neuralgia, neuropathy, nystagmus, paralysis,
1097 vertigo; rare were ataxia, coma, diplopia, dyskinesia, hostility, paranoid reaction, torticollis,
1098 withdrawal syndrome; also observed were abnormal gait, akathisia, akinesia, aphasia,
1099 choreoathetosis, circumoral paresthesia, delirium, delusions, dysarthria, euphoria, extrapyramidal
1100 syndrome, fasciculations, grand mal convulsion, hyperalgesia, irritability, manic reaction,
1101 manic-depressive reaction, meningitis, myelitis, peripheral neuritis, psychosis, psychotic
1102 depression, reflexes decreased, reflexes increased, stupor, trismus.

1103 **Respiratory System:** Frequent were pharyngitis; infrequent were asthma, dyspnea,
1104 epistaxis, laryngitis, pneumonia; rare were stridor; also observed were dysphonia, emphysema,
1105 hemoptysis, hiccups, hyperventilation, lung fibrosis, pulmonary edema, respiratory flu, sputum
1106 increased.

1107 **Skin and Appendages:** Frequent were rash; infrequent were acne, alopecia, dry skin,
1108 eczema, pruritus, urticaria; rare were exfoliative dermatitis, furunculosis, pustular rash,
1109 seborrhea; also observed were angioedema, ecchymosis, erythema multiforme, erythema
1110 nodosum, hirsutism, maculopapular rash, skin discoloration, skin hypertrophy, skin ulcer,
1111 sweating decreased, vesiculobullous rash.

1112 **Special Senses:** Infrequent were conjunctivitis, earache, keratoconjunctivitis, mydriasis,
1113 photophobia, retinal hemorrhage, tinnitus; rare were blepharitis, visual field defect; also observed
1114 were amblyopia, anisocoria, blurred vision, cataract, conjunctival edema, corneal ulcer, deafness,
1115 exophthalmos, glaucoma, hyperacusis, night blindness, parosmia, ptosis, taste loss.

1116 **Urogenital System:** Frequent were dysmenorrhea; infrequent were albuminuria,
1117 amenorrhea*, breast pain*, cystitis, dysuria, prostatitis*, urinary retention; rare were breast
1118 enlargement*, breast neoplasm*, female lactation, hematuria, kidney calculus, metrorrhagia*,
1119 nephritis, nocturia, pregnancy and puerperal disorders*, salpingitis, urinary incontinence, uterine
1120 fibroids enlarged*; also observed were breast atrophy, ejaculatory disturbance, endometrial
1121 disorder, epididymitis, fibrocystic breast, leukorrhea, mastitis, oliguria, polyuria, pyuria,
1122 urethritis, urinary casts, urinary urgency, urolith, uterine spasm, vaginal hemorrhage.

1123 *Based on the number of men and women as appropriate.

1124 **Postmarketing Reports:** Voluntary reports of adverse events in patients taking
1125 immediate-release paroxetine hydrochloride that have been received since market introduction
1126 and not listed above that may have no causal relationship with the drug include acute
1127 pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis,
1128 and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré
1129 syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion,
1130 symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome-like

1131 events, serotonin syndrome; extrapyramidal symptoms which have included akathisia,
1132 bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been
1133 associated with concomitant use of pimozide; tremor and trismus; status epilepticus, acute renal
1134 failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic
1135 neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including torsade de pointes),
1136 thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including
1137 aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic
1138 syndromes (such as Henoch-Schönlein purpura). There has been a case report of an elevated
1139 phenytoin level after 4 weeks of immediate-release paroxetine and phenytoin coadministration.
1140 There has been a case report of severe hypotension when immediate-release paroxetine was
1141 added to chronic metoprolol treatment.

1142 **DRUG ABUSE AND DEPENDENCE**

1143 **Controlled Substance Class:** PAXIL CR is not a controlled substance.

1144 **Physical and Psychologic Dependence:** PAXIL CR has not been systematically studied
1145 in animals or humans for its potential for abuse, tolerance or physical dependence. While the
1146 clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were
1147 not systematic and it is not possible to predict on the basis of this limited experience the extent to
1148 which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently,
1149 patients should be evaluated carefully for history of drug abuse, and such patients should be
1150 observed closely for signs of misuse or abuse of PAXIL CR (e.g., development of tolerance,
1151 incrementations of dose, drug-seeking behavior).

1152 **OVERDOSAGE**

1153 **Human Experience:** Since the introduction of immediate-release paroxetine hydrochloride in
1154 the United States, 342 spontaneous cases of deliberate or accidental overdose during
1155 paroxetine treatment have been reported worldwide (circa 1999). These include overdoses with
1156 paroxetine alone and in combination with other substances. Of these, 48 cases were fatal and of
1157 the fatalities, 17 appeared to involve paroxetine alone. Eight fatal cases that documented the
1158 amount of paroxetine ingested were generally confounded by the ingestion of other drugs or
1159 alcohol or the presence of significant comorbid conditions. Of 145 non-fatal cases with known
1160 outcome, most recovered without sequelae. The largest known ingestion involved 2,000 mg of
1161 paroxetine (33 times the maximum recommended daily dose) in a patient who recovered.

1162 Commonly reported adverse events associated with paroxetine overdose include
1163 somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other
1164 notable signs and symptoms observed with overdoses involving paroxetine (alone or with other
1165 substances) include mydriasis, convulsions (including status epilepticus), ventricular
1166 dysrhythmias (including torsade de pointes), hypertension, aggressive reactions, syncope,
1167 hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction
1168 (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin
1169 syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

1170 **Overdosage Management:** Treatment should consist of those general measures employed in
1171 the management of overdosage with any drugs effective in the treatment of major depressive
1172 disorder.

1173 Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital
1174 signs. General supportive and symptomatic measures are also recommended. Induction of emesis
1175 is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway
1176 protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic
1177 patients.

1178 Activated charcoal should be administered. Due to the large volume of distribution of this
1179 drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of
1180 benefit. No specific antidotes for paroxetine are known.

1181 A specific caution involves patients taking or recently having taken paroxetine who might
1182 ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the
1183 parent tricyclic and an active metabolite may increase the possibility of clinically significant
1184 sequelae and extend the time needed for close medical observation (see PRECAUTIONS—
1185 *Drugs Metabolized by Cytochrome CYP2D6*).

1186 In managing overdosage, consider the possibility of multiple-drug involvement. The physician
1187 should consider contacting a poison control center for additional information on the treatment of
1188 any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians'*
1189 *Desk Reference* (PDR).

1190 **DOSAGE AND ADMINISTRATION**

1191 **Major Depressive Disorder: Usual Initial Dosage:** PAXIL CR should be administered as
1192 a single daily dose, usually in the morning, with or without food. The recommended initial dose
1193 is 25 mg/day. Patients were dosed in a range of 25 mg to 62.5 mg/day in the clinical trials
1194 demonstrating the effectiveness of PAXIL CR in the treatment of major depressive disorder. As
1195 with all drugs effective in the treatment of major depressive disorder, the full effect may be
1196 delayed. Some patients not responding to a 25-mg dose may benefit from dose increases, in
1197 12.5-mg/day increments, up to a maximum of 62.5 mg/day. Dose changes should occur at
1198 intervals of at least 1 week.

1199 Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be
1200 swallowed whole.

1201 **Maintenance Therapy:** There is no body of evidence available to answer the question of
1202 how long the patient treated with PAXIL CR should remain on it. It is generally agreed that acute
1203 episodes of major depressive disorder require several months or longer of sustained
1204 pharmacologic therapy. Whether the dose of an antidepressant needed to induce remission is
1205 identical to the dose needed to maintain and/or sustain euthymia is unknown.

1206 Systematic evaluation of the efficacy of immediate-release paroxetine hydrochloride has
1207 shown that efficacy is maintained for periods of up to 1 year with doses that averaged about

1208 30 mg, which corresponds to a 37.5-mg dose of PAXIL CR, based on relative bioavailability
1209 considerations (see CLINICAL PHARMACOLOGY—Pharmacokinetics).
1210 **Panic Disorder: Usual Initial Dosage:** PAXIL CR should be administered as a single daily
1211 dose, usually in the morning. Patients should be started on 12.5 mg/day. Dose changes should
1212 occur in 12.5-mg/day increments and at intervals of at least 1 week. Patients were dosed in a
1213 range of 12.5 to 75 mg/day in the clinical trials demonstrating the effectiveness of PAXIL CR.
1214 The maximum dosage should not exceed 75 mg/day.
1215 Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be
1216 swallowed whole.
1217 **Maintenance Therapy:** Long-term maintenance of efficacy with the immediate-release
1218 formulation of paroxetine was demonstrated in a 3-month relapse prevention trial. In this trial,
1219 patients with panic disorder assigned to immediate-release paroxetine demonstrated a lower
1220 relapse rate compared to patients on placebo. Panic disorder is a chronic condition, and it is
1221 reasonable to consider continuation for a responding patient. Dosage adjustments should be
1222 made to maintain the patient on the lowest effective dosage, and patients should be periodically
1223 reassessed to determine the need for continued treatment.
1224 **Social Anxiety Disorder: Usual Initial Dosage:** PAXIL CR should be administered as a
1225 single daily dose, usually in the morning, with or without food. The recommended initial dose is
1226 12.5 mg/day. Patients were dosed in a range of 12.5 mg to 37.5 mg/day in the clinical trial
1227 demonstrating the effectiveness of PAXIL CR in the treatment of social anxiety disorder. If the
1228 dose is increased, this should occur at intervals of at least 1 week, in increments of 12.5 mg/day,
1229 up to a maximum of 37.5 mg/day.
1230 Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be
1231 swallowed whole.
1232 **Maintenance Therapy:** There is no body of evidence available to answer the question of
1233 how long the patient treated with PAXIL CR should remain on it. Although the efficacy of
1234 PAXIL CR beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials,
1235 social anxiety disorder is recognized as a chronic condition, and it is reasonable to consider
1236 continuation of treatment for a responding patient. Dosage adjustments should be made to
1237 maintain the patient on the lowest effective dosage, and patients should be periodically
1238 reassessed to determine the need for continued treatment.
1239 **Premenstrual Dysphoric Disorder: Usual Initial Dosage:** PAXIL CR should be
1240 administered as a single daily dose, usually in the morning, with or without food. PAXIL CR
1241 may be administered either daily throughout the menstrual cycle or limited to the luteal phase of
1242 the menstrual cycle, depending on physician assessment. The recommended initial dose is
1243 12.5 mg/day. In clinical trials, both 12.5 mg/day and 25 mg/day were shown to be effective.
1244 Dose changes should occur at intervals of at least 1 week.
1245 Patients should be cautioned that PAXIL CR should not be chewed or crushed, and should be
1246 swallowed whole.

1247 **Maintenance/Continuation Therapy:** The effectiveness of PAXIL CR for a period
1248 exceeding 3 menstrual cycles has not been systematically evaluated in controlled trials.
1249 However, women commonly report that symptoms worsen with age until relieved by the onset of
1250 menopause. Therefore, it is reasonable to consider continuation of a responding patient. Patients
1251 should be periodically reassessed to determine the need for continued treatment.
1252 **Special Populations: Treatment of Pregnant Women During the Third Trimester:**
1253 Neonates exposed to PAXIL CR and other SSRIs or SNRIs, late in the third trimester have
1254 developed complications requiring prolonged hospitalization, respiratory support, and tube
1255 feeding (see WARNINGS). When treating pregnant women with paroxetine during the third
1256 trimester, the physician should carefully consider the potential risks and benefits of treatment.
1257 The physician may consider tapering paroxetine in the third trimester.
1258 **Dosage for Elderly or Debilitated Patients, and Patients With Severe Renal or**
1259 **Hepatic Impairment:** The recommended initial dose of PAXIL CR is 12.5 mg/day for elderly
1260 patients, debilitated patients, and/or patients with severe renal or hepatic impairment. Increases
1261 may be made if indicated. Dosage should not exceed 50 mg/day.
1262 **Switching Patients to or From a Monoamine Oxidase Inhibitor:** At least 14 days
1263 should elapse between discontinuation of an MAOI and initiation of therapy with PAXIL CR.
1264 Similarly, at least 14 days should be allowed after stopping PAXIL CR before starting an MAOI.
1265 **Discontinuation of Treatment With PAXIL CR:** Symptoms associated with discontinuation
1266 of immediate-release paroxetine hydrochloride or PAXIL CR have been reported (see
1267 PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing
1268 treatment, regardless of the indication for which PAXIL CR is being prescribed. A gradual
1269 reduction in the dose rather than abrupt cessation is recommended whenever possible. If
1270 intolerable symptoms occur following a decrease in the dose or upon discontinuation of
1271 treatment, then resuming the previously prescribed dose may be considered. Subsequently, the
1272 physician may continue decreasing the dose but at a more gradual rate.

1273 **HOW SUPPLIED**

1274 PAXIL CR is supplied as an enteric film-coated, controlled-release, round tablet, as follows:
1275 12.5-mg yellow tablets, engraved with PAXIL CR and 12.5
1276 NDC 0029-3206-13 Bottles of 30
1277 25-mg pink tablets, engraved with PAXIL CR and 25
1278 NDC 0029-3207-13 Bottles of 30
1279 37.5 mg blue tablets, engraved with PAXIL CR and 37.5
1280 NDC 0029-3208-13 Bottles of 30
1281 Store at or below 25°C (77°F) [see USP].
1282
1283 PAXIL CR is a registered trademark of GlaxoSmithKline.
1284 GEOMATRIX is a trademark of Jago Pharma, Muttens, Switzerland.
1285

Medication Guide

PAXIL CR® (PAX-il) (paroxetine hydrochloride) Controlled-Release Tablets
About Using Antidepressants in Children and Teenagers

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

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

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

1. There is a Risk of Suicidal Thoughts or Actions

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

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

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

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

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

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

2. How to Try to Prevent Suicidal Thoughts and Actions

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

- 1331 Whenever an antidepressant is started or its dose is changed, pay close attention to your child.
1332 After starting an antidepressant, your child should generally see his or her healthcare provider:
1333 • Once a week for the first 4 weeks
1334 • Every 2 weeks for the next 4 weeks
1335 • After taking the antidepressant for 12 weeks
1336 • After 12 weeks, follow your healthcare provider's advice about how often to come back
1337 • More often if problems or questions arise (see Section 3)

1338
1339 You should call your child's healthcare provider between visits if needed.
1340

1341 3. You Should Watch for Certain Signs If Your Child is Taking an Antidepressant

1342

1343 Contact your child's healthcare provider *right away* if your child exhibits any of the following
1344 signs for the first time, or if they seem worse, or worry you, your child, or your child's teacher:

- 1345 • Thoughts about suicide or dying
1346 • Attempts to commit suicide
1347 • New or worse depression
1348 • New or worse anxiety
1349 • Feeling very agitated or restless
1350 • Panic attacks
1351 • Difficulty sleeping (insomnia)
1352 • New or worse irritability
1353 • Acting aggressive, being angry, or violent
1354 • Acting on dangerous impulses
1355 • An extreme increase in activity and talking
1356 • Other unusual changes in behavior or mood

1357
1358 Never let your child stop taking an antidepressant without first talking to his or her healthcare
1359 provider. Stopping an antidepressant suddenly can cause other symptoms.
1360

1361 4. There are Benefits and Risks When Using Antidepressants

1362

1363 Antidepressants are used to treat depression and other illnesses. Depression and other illnesses
1364 can lead to suicide. In some children and teenagers, treatment with an antidepressant increases
1365 suicidal thinking or actions. It is important to discuss all the risks of treating depression and also
1366 the risks of not treating it. You and your child should discuss all treatment choices with your
1367 healthcare provider, not just the use of antidepressants.

1368
1369 Other side effects can occur with antidepressants (see section below).
1370

1371 Of all the antidepressants, only fluoxetine (Prozac®)* has been FDA approved to treat pediatric
1372 depression.
1373

1374 For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine
1375 (Prozac®)*, sertraline (Zoloft®)*, fluvoxamine, and clomipramine (Anafranil®)*.
1376
1377 Your healthcare provider may suggest other antidepressants based on the past experience of your
1378 child or other family members.
1379
1380 Is this all I need to know if my child is being prescribed an antidepressant?
1381
1382 No. This is a warning about the risk for suicidality. Other side effects can occur with
1383 antidepressants. Be sure to ask your healthcare provider to explain all the side effects of the
1384 particular drug he or she is prescribing. Also ask about drugs to avoid when taking an
1385 antidepressant. Ask your healthcare provider or pharmacist where to find more information.
1386
1387
1388 *The following are registered trademarks of their respective manufacturers: Prozac®/Eli Lilly
1389 and Company; Zoloft®/Pfizer Pharmaceuticals; Anafranil®/Mallinckrodt Inc.
1390
1391
1392 This Medication Guide has been approved by the U.S. Food and Drug Administration for all
1393 antidepressants.
1394
1395 January 2005 MG-PC:1
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1403 April/December 2006 PC:LXX+9