

## Effect of *Paxil CR* and *Paxil* on Suicidal Ideation and Behavior in Adults

This response may include reference to information about Paxil CR® (paroxetine HCl) Controlled-Release Tablets; Paxil® (paroxetine HCl).

### SUMMARY

- The prescribing information for *Paxil* and *Paxil CR* (as with all antidepressants approved for the treatment of major depressive disorder (MDD)) contains a black box warning outlining an increased risk of suicidal thoughts and behavior in children, adolescents, and young adults (18 - 24 years of age) treated with antidepressant medications and emphasizes the need for close monitoring of all patients started on these medications. This labeling also contains language about the need to monitor all patients, including adults, for suicidal behavior or thinking.
- A recent analysis by GSK of placebo controlled trials in 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  $\geq 65$  years), no such increase was observed. In adults with MDD (all ages), there was a statistically significant increase in the frequency of suicidal behavior 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.
- Based on the above findings, GSK believes that young adults, especially those with MDD, may be at increased risk for suicidal behavior during treatment with paroxetine.
- It is difficult to conclude a causal relationship between paroxetine and suicidality in adults due to the small incidence and absolute number of events, the retrospective nature of the analyses, and potential for confounding by the fact that the events of interest are a symptom of the psychiatric illnesses themselves.
- The clinical trial data regarding adult suicidal behavior conducted by GSK have been posted to the company website, [www.gsk.com](http://www.gsk.com). Additionally, this letter is available on the website with cross-references to documents, also on the website, related to the current analysis.
- Important Safety information is found in the attached Prescribing Information.
- The prescribing information for this product contains a boxed warning. Please consult the WARNING section of the attached prescribing information for further details and for important safety information.

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### BOXED WARNING

#### Suicidality and Antidepressant Drugs

**Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of *PAXIL CR* or *PAXIL* or any other antidepressant in a child, adolescent, or young adults must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all**

ages who are started on antidepressant therapy should be 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* and *PAXIL* are not approved for use in pediatric patients. (See **WARNINGS: Clinical Worsening and Suicide Risk**, **PRECAUTIONS: Information for Patients** and **PRECAUTIONS: Pediatric Use**.)

## BACKGROUND

Since market introduction, there have been reports in the published literature and GlaxoSmithKline has received spontaneous reports of suicide, suicide attempts, and suicidal ideation during therapy with paroxetine. Because of the significant background incidence of suicide among patients with depression and the presence of other confounding factors, no causal association can be drawn from these reports.

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. In addition, patients with a history of suicidal behavior or thoughts, those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at an increased risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

**NOTE: See **WARNINGS: Clinical Worsening and Suicide Risk** section of the attached prescribing information** <sup>(1, 2, 3)</sup>

## CLINICAL INFORMATION

Several analyses conducted by GlaxoSmithKline have evaluated the question of whether there is an increased risk of suicidality (suicidal thinking or behavior). Until most recently, these analyses of paroxetine's potential association with treatment-emergent suicidality did not produce evidence suggestive of an association in adults. <sup>(4)</sup> In these previous studies, a difference in suicidality between paroxetine and placebo was reported in young adults, but the difference was not statistically significant. However, the most recent analyses, while not statistically significant, show a larger difference between paroxetine and placebo in the young adult population, one that is fairly consistent across psychiatric disorders (MDD and non-MDD). <sup>(5)</sup>

In addition, reports in the published literature have expressed varied views as to paroxetine's effect on suicidal thinking or behavior compared with placebo or other antidepressants. <sup>(6) (7) (8, 9, 10, 11) (12) (13) (14) (15) (16) (17, 18)</sup>

## GSK POOLED ANALYSES

In addition to the pooled analysis required under Article 31 (a European-regulatory clause for assessing safety of medications) as described later <sup>(4)</sup>, GSK more recently conducted an analysis of paroxetine, which included data from short- and long-term placebo-controlled trials in adults. <sup>(5)</sup> The most recent analysis was conducted in two portions: trials that included patients with MDD and trials that included patients with other psychiatric diagnoses (anxiety disorders and non-MDD depressive disorders). A total of 57 trials were evaluated overall for all indications, including 19 trials specific to MDD. The results of this analysis found:

- Across all disorders, a higher frequency of suicidal behavior in young adults (prospectively defined as aged 18-24 years) treated with paroxetine compared with placebo (17/776 [2.19%] versus 5/542

[0.92%]), although this difference was not statistically significant. In the older age groups (aged 25-64 years and  $\geq 65$  years), no such increase was observed.

- In adults with MDD (all ages), a statistically significant increase in the frequency of suicidal behavior in patients treated with paroxetine compared with placebo (11/3455 [0.32%] versus 1/1978 [0.05%]). 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. Of these paroxetine-treated patients with suicidal behavior, 10 of 11 had experienced improvement in their major depression and 9 of 11 had an identified social stressor at the time of the suicide attempt.

For a summary of the events of suicidal behavior and treatment response, see Tables 1 and 2, respectively.

**Table 1. Summary of Events of Suicidal Behavior by Study Population, Treatment Group, and Age Band\* (5)**

Group	18-24 year olds			25-64 year olds		
	PAR	PBO	OR (95% CI)	PAR	PBO	OR (95% CI)
All Indications	17/776 (2.19%)	5/542 (0.92%)	2.4 (0.9, 7.3)	32/7543 (0.42%)	34/5000 (0.68%)	0.6 (0.4, 1.0)
Major Depressive Disorder†	3/230 (1.30%)	0/104 (0.00%)	Inf (0.3, Inf)	8/2713 (0.29%)	0/1567 (0.00%)	Inf (1.3, Inf)
Intermittent Brief Depression	10/35 (28.57%)	5/38 (13.61%)	2.6 (0.8, 9.4)	22/112 (19.64%)	30/113 (26.55%)	0.7 (0.4, 1.3)
All Non-Depression	4/504 (0.79%)	0/393 (0.00%)	Inf (0.7, Inf)	2/4612 (0.04%)	4/3202 (0.12%)	0.3 (0.0, 2.0)
Panic Disorder	1/121 (0.83%)	0/117 (0.00%)	Inf (0.1, Inf)	0/962 (0.00%)	2/782 (0.26%)	0.0 (0.0, 2.8)
Obsessive Compulsive Disorder	1/87 (1.15%)	0/51 (0.00%)	Inf (0.00, Inf)	1/568 (0.18%)	1/346 (0.29%)	0.6 (0.0, 23.8)
Social Anxiety Disorder	2/114 (1.75%)	0/89 (0.00%)	Inf (0.2, Inf)	0/825 (0.00%)	1/542 (0.18%)	0.0 (0.0, 12.5)
Posttraumatic Stress Disorder	0/51 (0.00%)	0/51 (0.00%)	not enough events	1/634 (0.16%)	0/447 (0.00%)	Inf (0.0, Inf)

Group	18-24 year olds	25-64 year olds
<p>PAR=Paroxetine; PBO=Placebo; Inf=infinite ; OR=Odds Ratio</p> <p>*The following study populations had no events of suicidal behavior: dysthymia, bipolar depression, generalized anxiety disorder, premenstrual dysphoric disorder, detoxification in alcoholics, and fibromyalgia. Full datasets, including data for other study endpoints, can be found at <a href="http://www.gsk.com">www.gsk.com</a>.</p> <p>†For events of suicidal behavior, all adult patients with MDD: Paroxetine, 11/3455 (0.32%); Placebo, 1/1978 (0.05%), OR 6.7 (95% CI 1.1, 149.4)</p>		

**Table 2. Number and Percentage of Patients with Treatment Response by Study Population, Treatment Group, and Age Band\* (5)**

Group	18-24 year olds			25-64 year olds		
	PAR	PBO	OR (95% CI)	PAR	PBO	OR (95% CI)
Major Depressive Disorder†	102/214 (47.66%)	45/98 (45.92%)	1.1 (0.7, 1.7)	1317/2525 (52.16%)	538/1497 (35.94%)	1.9 (1.7, 2.2)
Panic Disorder‡	87/115 (75.65%)	61/113 (53.98%)	2.6 (1.5, 4.7)	622/919 (67.68%)	356/765 (46.54%)	2.4 (2.0, 2.9)
Obsessive Compulsive Disorder‡	30/84 (35.71%)	16/51 (31.37%)	1.2 (0.6, 2.6)	212/549 (38.62%)	73/342 (21.35%)	2.3 (1.7, 3.2)
Social Anxiety Disorder‡	63/106 (59.43%)	26/86 (30.23%)	3.4 (1.8, 6.2)	421/792 (53.16%)	167/535 (31.21%)	2.5 (2.0, 3.1)
Generalized Anxiety Disorder	63/99 (63.64%)	34/66 (51.52%)	1.6 (0.9, 3.1)	474/724 (65.47%)	278/569 (48.86%)	2.0 (1.6, 2.5)
Posttraumatic Stress Disorder‡	27/48 (56.25%)	21/48 (43.75%)	1.6 (0.7, 3.7)	339/580 (58.45%)	167/427 (39.11%)	2.2 (1.7, 2.8)
Premenstrual Dysphoric Disorder‡	10/20 (50.00%)	5/13 (38.46%)	1.6 (0.4, 7.1)	452/651 (69.43%)	158/372 (42.47%)	3.1 (2.4, 4.0)

Group	18-24 year olds	25-64 year olds
<p>PAR=Paroxetine; PBO=Placebo; OR=Odds Ratio</p> <p>*Presented are response rates for indications that are FDA approved for <i>Paxil</i> and/or <i>Paxil CR</i>. Full datasets, including data for other study endpoints, can be found at <a href="http://www.gsk.com">www.gsk.com</a>.</p> <p>†Response is defined as <math>\geq 50\%</math> reduction in total score on either the HAMD or MADRS</p> <p>‡Response is defined as Clinical Global Impression (CGI) of Very Much Improved or Much Improved at last observation carried forward (LOCF) endpoint</p>		

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<sup>(4)</sup> or in GSK's prior analyses of suicide attempts.<sup>(19)</sup> In the Article 31 analysis of self-harm in patients with depressive illness (including MDD and non-MDD 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 for MDD. A separate analysis was conducted for non-MDD indications. 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 of the MDD population. 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 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.

With respect to the current GSK analysis, in placebo-controlled 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. 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 disorders other than depressive disorders (0.99% for paroxetine versus 0.25% for placebo). This finding was consistent across the non-MDD indications.

### Article 31 Referral

In 2003, the UK Medicines and Healthcare products Regulatory Agency (MHRA) referred paroxetine to the EMEA for an EU-level review under Article 31 of the Community Code on Human Medicines. 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 first set of analyses to the initial Article 31 questions in September 2003, the second set in January 2004, and the third in March 2004.<sup>(4)</sup> Post-hoc analyses of the placebo-controlled and active-controlled GSK studies of *Paxil* and *Paxil CR* (57 total studies, including 19 depression studies) were conducted to evaluate adverse events possibly related to suicidal behavior in response to Article 31. Run-in and uncontrolled extension phases were not included, owing to the presence of multiple confounding factors. The methodology utilized to identify subjects included in the "possibly related to suicidal behavior" category departed from the conventional methods of reviewing

adverse event data. The method employed was a blinded database search of any and all patients who reported events possibly related to suicidal thinking and/or behavior (e.g. self-injurious remarks or behaviors related to suicidal ideation, suicide attempts, self-inflicted harm or overdose). Subjects with post-randomization suicide attempts and subjects with new or worsening suicidal ideation occurring after randomization were included in the analyses. These analyses of adverse events possibly related to suicidal behavior were not prospectively designed. As all relevant and potentially contributing clinical factors therefore can not be taken into account, use of different analytic methods may produce different results.

Analysis of suicide-related events by age for adult placebo-controlled trials showed that there was a greater incidence for the paroxetine treatment group (1.8%) compared to the placebo group (1.4%) in young adults 18-29 years of age, but this difference was not statistically significant (OR 1.28; 95% CI 0.7, 2.32;  $P = 0.46$ ).<sup>(4)</sup> Of the events outlined below for the overall adult population, 31/66 (47%) in the paroxetine group and 17/55 (31%) in the placebo group occurred the 18-29 age group.

In the pooled analyses of the adult placebo-controlled trials there were 4 completed suicides; 1 in the paroxetine treatment group (during the on-therapy period) and 3 in the placebo group (all in the post-treatment period). In the adult placebo-controlled analyses, no differences on adverse event reporting, were seen between paroxetine and placebo in suicidal thinking and suicide attempts.<sup>(4)</sup> There were 2 treatment period analyses (on therapy and on therapy plus 30-day follow-up). The incidence of adverse events possibly related to suicidal behavior while on therapy (treatment phase plus taper phase) was 0.8% (66/8481) for paroxetine and 0.9% (55/5808) for placebo in the overall population. The incidence of adverse events possibly related to suicidal behavior while on therapy plus 30 days of follow-up (treatment phase, taper phase and follow-up period) was 1.1% (92/8481) for paroxetine and 1.1% (63/5808) for placebo.

In the pooled analyses of the adult, active-controlled trials there were 10 completed suicides; 5 in the paroxetine treatment group (1 on-therapy and 4 post-therapy) and 5 in the comparator group (2 on-therapy and 3 post-therapy).<sup>(4)</sup> The incidence of adverse events possibly related to suicidal behavior while on therapy was 0.8% (55/6522) for paroxetine and 1.3% (63/4969) for active comparator in the overall population. The incidence of adverse events possibly related to suicidal behavior while on therapy plus 30 days of follow-up was 1.2% (79/6522) for paroxetine and 1.5% (76/4969) for active comparator. In the adult, active-controlled on therapy analyses, there was a lower incidence of events possibly related to suicidal behavior in the group treated with paroxetine compared with active control; this difference was statistically significant ( $P = 0.031$ ). In the adult, active-controlled on therapy plus 30 days analyses, there were no statistically significant differences seen in the incidence of events possibly related to suicidal behavior.

In the adult, uncontrolled trials for paroxetine, there were 3 completed suicides (2 on-therapy and 1 post-therapy). Overall, the incidence of adverse events possibly related to suicidal behavior while on therapy (treatment phase plus taper phase) was 0.8% (42/5448) for paroxetine. The incidence of adverse events possibly related to suicidal behavior while on therapy plus 30 days of follow-up (treatment phase, taper phase and follow-up period) was 1.1% (58/5448) for paroxetine.

Analyses of the HAM-D depression rating scale suicide item 3 utilized in the adult depression placebo-controlled and active-controlled trials were conducted.<sup>(4)</sup> A subset of patients from the adult depression placebo-controlled and active-controlled studies defined as having no suicidal ideation at study entry were included in the analyses examining “emergent suicidal ideation” based on item 3 (suicide) of the HAM-D.<sup>(4)</sup> In these analyses, “emergent suicidal ideation” was defined as having a baseline score of 0 or 1 for the HAM-D item 3 which increased to  $\geq 3$  at any post-baseline assessment. Results from the analyses demonstrated that there were no statistically significant differences between paroxetine and placebo or paroxetine and active control in the number of patients with treatment-emergent suicidal ideation.

Change from baseline in item 3 of the HAM-D was also examined in the adult depression placebo-controlled and active-controlled trials. In the adult, placebo-controlled trials, a statistically significant difference of -0.17 in favor of paroxetine was seen in the change from baseline to endpoint on item 3 of

HAM-D ( $P < 0.01$ ). In the adult active-controlled trials, a statistically significant difference of -0.06 in favor of paroxetine was seen in the change from baseline to endpoint on item 3 of HAM-D ( $P < 0.01$ ).

Change from baseline in item 10 of the Montgomery Asberg Depression Rating Scale (MADRS) was also examined in the adult depression placebo-controlled and active-controlled trials. <sup>(4)</sup> In the adult, placebo-controlled trials, a statistically significant difference of -0.2 in favor of paroxetine was seen in the change from baseline to endpoint on item 10 of MADRS ( $P < 0.01$ ). In the adult, active-controlled trials, no significant difference between the paroxetine and active comparator group was observed.

## RETROSPECTIVE DATABASE REVIEWS

A retrospective, observational, cohort study and nested, case-control study were conducted using the UK General Practice Research Database (GPRD) between 1988 and 2003. <sup>(19)</sup> In the cohort analysis, there were no statistically significant differences in suicidal behavior risk between SSRI and non-SSRI users or between users of paroxetine and other SSRIs (individually and in aggregate) in adult patients. In the nested-case control analysis there was a significant decrease in suicidal behavior associated with SSRI use among adult patients and a small, but not statistically significant, increased risk associated with paroxetine use relative to other SSRI use (adjusted OR = 1.08, 95% CI: 0.87-1.34). There was no significant interaction between suicidal behavior, duration and treatment associated with SSRI use relative to non-SSRI use, or paroxetine use relative to use of other SSRIs.

In the cohort analysis, relative to non-SSRI antidepressant users, SSRI users had a greater history of medical events, including prior suicidal behavior, psychiatric referral and psychosis that were likely to increase their risk of suicidal behavior. Compared to users of all other SSRIs combined, users of paroxetine were significantly more likely to have had a history of prior psychiatry referral and insomnia. Patients treated with paroxetine aged 18 years and under had an even greater history of these factors which may increase the risk of suicidal behavior. After adjusting for these patient factors up to the time of initiation of therapy in the cohort analysis, there were no statistically significant differences in suicidal behavior risk between SSRI and non-SSRI users (HR = 0.96, 95% CI: 0.85-1.08) or between users of paroxetine and other SSRIs (individually and in aggregate) in adult patients. For patients aged 10 to 18 years, there was a statistically significant increase in risk for SSRI users relative to non-SSRI users (HR = 1.90, 95% CI: 1.29-2.8), and for users of paroxetine relative to other SSRIs combined (HR = 1.58, 95% CI: 1.17-2.14).

In the nested-case control analysis, after adjusting for patient history, among adult patients there was a significant decrease in suicidal behavior associated with SSRI use (adjusted OR = 0.84, 95% CI: 0.71-0.99) and a small, but not statistically significant, increased risk associated with paroxetine use relative to other SSRI use (adjusted OR = 1.08, 95% CI: 0.87-1.34). There was no significant interaction between suicidal behavior, duration and treatment associated with SSRI use relative to non-SSRI use, or paroxetine use relative to use of other SSRIs. Among patients aged 10 to 18 years, results showed a significantly increased risk associated with SSRI use relative to non-SSRI use (OR = 1.82, 95% CI: 1.04-3.21). There was an elevated, but not statistically significant, risk associated with paroxetine use relative to use of all other SSRIs (OR = 1.39, 95% CI: 0.89-2.16). Among patients aged 10 to 18 years, there was no significant interaction between suicidal behavior risk, duration of therapy, and SSRI use relative to non-SSRI use. The analysis found increased risk with different durations of exposure but no trend associated with increasing duration of medication use. In this population, results for paroxetine use relative to use of other SSRIs were comparable.

A matched case-control study in adults (19 - 64 years) compared the risk of suicide attempts and completed suicides after inpatient treatment for a depressive disorder. <sup>(20)</sup> There was a high and comparable level of disease severity in both the cases (suicide attempts and completed suicides) and controls (no suicide attempt and no completed suicide) groups. Cases and controls were compared in 3 ways: 1) treatment with any antidepressant versus no antidepressant, 2) SSRIs and other individual antidepressant treatment compared to no antidepressant treatment, 3) individual SSRIs compared to no antidepressant.

Suicide attempts and completed suicides were not significantly higher in adults treated with antidepressants compared to no antidepressant treatment (OR, 1.10; 95% CI, 0.86 - 1.39,  $P = 0.46$  [521 cases and 2394 controls]) and (OR, 0.9; 95% CI, 0.52 - 1.55,  $P = 0.7$ , [86 cases and 396 controls]), respectively. SSRIs as a group did not significantly increase the risk of suicide attempts (OR, 0.97; 95% CI, 0.72 - 1.30,  $P = 0.72$ ) or completed suicides (OR, 0.87; 95% CI, 0.44 - 1.73,  $P = 0.83$ ). Adults treated with paroxetine did not have a significantly increased risk of suicide attempts (OR, 1.07; 95% CI, 0.71 - 1.60,  $P = 0.5$ ) or completed suicides (OR, 0.93; 95% CI, 0.37 - 2.32,  $P = 0.93$ ) compared to patients with no antidepressant treatment.

#### **Enclosure: Prescribing Information for *Paxil CR* Tablets**

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**Some information contained in this response may not be included in the approved Prescribing information. This response is not intended to offer recommendations for administering this product in a manner inconsistent with its approved labeling. Please note that reports of adverse events in the published literature often lack causality assessments and may contain incomplete information; therefore, conclusions about causality generally cannot be drawn.**

**In order for GlaxoSmithKline to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the attached Prescribing Information.**

**This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.**

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