

Use of *Paxil Tablets* or *Paxil CR Tablets* in Pediatric Patients

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

SUMMARY

- GlaxoSmithKline (GSK) has conducted several trials in pediatric patients treated with *Paxil Tablets*; no studies in pediatric patients treated with *Paxil CR Tablets* have been conducted. In 3 GSK studies for treatment of major depressive disorder (MDD) in pediatric patients, treatment with *Paxil Tablets* was not statistically superior to placebo with respect to efficacy. Children receiving *Paxil Tablets* had greater drop-out rates due to adverse events than adolescents receiving *Paxil Tablets*. Serious emotional lability, which may include suicidal thinking and/or behaviors, was more common in adolescents treated with *Paxil*.
- In 2 GSK studies for obsessive-compulsive disorder (OCD) and 1 social anxiety disorder study in pediatric patients, treatment with *Paxil Tablets* was statistically superior to placebo in only 2 of the 3 studies (1 OCD study [704] and 1 social anxiety disorder study [676]). Suicide attempt/ideation/thought and manic reaction were adverse events that lead to withdrawal in several patients treated with *Paxil Tablets*. Behavior activation/hyperactivity type adverse events were more likely to occur in children (<12 years) than in adolescents (12 to 17 years).
- No patients committed suicide in any of the GSK pediatric trials with *Paxil Tablets* and blinded expert panel reviews. A difference in adverse event reporting was seen between *Paxil Tablets* and placebo in suicidal thinking and suicide attempts for the pooled analyses of pediatric trials (>1,100 patients; aged 7 to 18 years). The incidence of adverse events possibly related to suicidal behavior while on therapy (treatment phase plus taper phase) was 2.4% (18/738) for *Paxil Tablets* and 1.1% (7/647) for placebo; and was 3.4% (25/738) in the *Paxil Tablets* group and 1.2% (8/647) in the placebo group 30 days after therapy. A blinded expert panel review of suicide-related events in children and adolescents (N = 1911; 5 randomized, double-blind trials [3 MDD, 1 OCD, and 1 social anxiety disorder]) found a significantly greater incidence of suicide-related events occurring in the *Paxil Tablets* group (22 of 642; 3.4%) compared to placebo (5 of 549; 0.9%; OR 3.86; 95% CI: 1.45, 10.26; $P = 0.003$).
- The pediatric clinical trial data for *Paxil Tablets* have been posted to the company website, www.gsk.com. Included on this website are clinical study reports conducted by GSK (synopses and full reports), a bibliography of pediatric publications/presentations, and this Medical Information letter.
- 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.

For additional labeling on suicidality and antidepressant drugs, please see the above-referenced WARNINGS and PRECAUTIONS sections in the attached prescribing information.

The FDA has issued a statement for the use of antidepressants in children, adolescents, and adults. Please visit this website for more information:
<http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm096273.htm>.

PUBLISHED LITERATURE

Six GSK-sponsored placebo-controlled trials have been conducted with *Paxil Tablets* (10 to 60 mg daily) in patients aged 7 to 18 years for the treatment of MDD, OCD, and social anxiety disorder.^(1,2,3,4,5,6) A preliminary retrospective review of *Paxil Tablets* treatment in pediatric patients with MDD has been conducted⁽⁷⁾, and an overview of the use of *Paxil Tablets* in the treatment of mood and anxiety disorders in pediatric patients has been published.⁽⁸⁾ In addition, a review of 6 placebo-controlled trials in pediatric patients (477 received treatment and 464 patients received placebo) treated with paroxetine, fluoxetine, sertraline, or venlafaxine for depression was published.⁽⁹⁾ In the same publication, a meta-analysis of 5 studies was conducted to evaluate selective serotonin reuptake inhibitors (SSRIs) by using the standardized mean difference as a measure of effect. The resultant effect size was small (0.26; 95% confidence interval [CI]: 0.13, 0.40). An effect size of 0.26 is equivalent to a 3 to 4 point difference on a scale that has a score range of 17 to 113. The author's discussion suggested various limitations of available data: short duration and follow-up periods, unlikely identification of serious adverse events, high rates of patient withdrawal, use of categorical outcomes (i.e. response and remission), unblinding the treatment group due to adverse events, and large placebo response rates. The authors questioned the quality of the individual studies and reported that the publications overstated the efficacy results and minimized the safety results.

Major Depressive Disorder

Study 329: An 8-week, double-blind, placebo-controlled, multi-center trial comparing the safety and efficacy of *Paxil Tablets* (20 to 40 mg daily; n = 93) and imipramine (200 to 300 mg daily; n = 95) with placebo (n = 87) in the treatment of adolescents (N = 275; 12 to 18 years) who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, (DSM-IV) criteria for MDD.^(1,10) At the protocol defined endpoint (Week 8), 190 patients completed the study, and there were no statistically significant mean changes from baseline in total Hamilton Rating Scale for Depression (HAM-D; primary endpoint) scores in both *Paxil Tablets* (-10.74; $P = 0.133$) and imipramine groups (-8.91; $P = 0.873$) compared to placebo (-9.09) in the last observation carried forward (LOCF) datasets. The percentage of responders with a $\geq 50\%$ reduction from baseline on the HAM-D also showed no change for patients assigned to *Paxil Tablets* (66.7%; $P = 0.112$) and imipramine (58.5%; $P = 0.612$) compared to placebo (55.2%). Patients experiencing remission (defined as HAM-D ≤ 8) showed a significant separation among those treated with *Paxil Tablets* (63.3%; $P = 0.019$) versus imipramine (50.0%; $P = 0.574$) compared to placebo (46.0%). The percentage of patients treated with *Paxil Tablets* who had Clinical Global Impression Improvement (CGI-I) scores of 1 or 2 (indicating very much improved or much improved) was 65.6% compared to 48.3% with placebo ($P = 0.020$), but mean change in CGI-I scores was not significant compared to placebo ($P = 0.094$). Imipramine treated patients showed no statistically significant change from baseline CGI-I as compared to placebo. Changes in baseline scores for the 9-item depression subscale of the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Lifetime version (K-SADS-L) were similar across treatment groups. Withdrawal from the study due to adverse events was 32% in the imipramine group, 10% in the *Paxil Tablets* group, and 7% in the placebo group. The most common adverse events ($\geq 5\%$ and twice the rate of placebo) during therapy with *Paxil Tablets* as compared to placebo included: somnolence (17.2% vs. 3.4%), insomnia (15.1% vs. 4.6%), tremor (10.8% vs. 2.3%), hostility (7.5% vs. 0%), emotional lability (6.5% vs. 1.1%), and tooth disorder (5.4% vs. 2.3%). Serious adverse events (defined as serious if it resulted in hospitalization, was associated with suicidal gestures, or was described by the treating physician as serious) occurred in 11 patients treated with *Paxil Tablets*, in 5 patients in the imipramine group, and 2 patients in the placebo group. The serious adverse events in patients treated with *Paxil Tablets* consisted of migraine headache during discontinuation taper (n = 1) and various psychiatric events (n = 10): emotional lability (e.g., suicidal ideation/gestures) (n = 5), conduct problems or hostility (e.g., aggressiveness, behavioral disturbance in school) (n = 2), worsening depression (n = 2), and euphoria/expansive mood (n = 1).

Study 329 long-term, continuation phase: After 8 weeks of the acute-phase treatment, a second phase of Study 329 was conducted where patients defined as responders (HAM-D ≤ 8 at week 8 or a $\geq 50\%$ decrease in HAM-D from baseline) could be continued on the same medication in a double-blind manner for a 6-month continuation treatment phase.⁽¹¹⁾ The objectives were to provide information on the safety

profile of *Paxil Tablets* and imipramine when given to adolescents for an extended period of time and to estimate the rate of relapse among responders maintained on treatment. The continuation phase of this study was not designed to analyze efficacy, as patients were not re-randomized at the end of the acute phase. The proportion of patients relapsing at any time during the continuation phase (regardless of HAM-D at endpoint) was 38.7% for the imipramine group, 36.4% for the *Paxil Tablets* group, and 23.1% for the placebo group. There were no significant differences between *Paxil Tablets* (13.5%) and placebo (18.2%) or between imipramine (15%) and placebo (18.2%) in withdrawals due to lack of efficacy.

Adverse events are presented in Table 1.⁽¹¹⁾ Serious adverse events during the continuation phase occurred in 9 patients (6 receiving *Paxil Tablets*, 2 on imipramine, and 1 on placebo). Serious events in patients receiving *Paxil Tablets* were peptic ulcer hemorrhage (n = 1), intentional overdose (n = 3), and manic reaction (n = 1); one patient experienced agitation, fatigue, nausea, drowsiness, and tremor after missing some doses of taper medication. In the imipramine group, 1 patient developed tricyclic toxicity and another took an intentional overdose. In the placebo group, 1 patient had homicidal and suicidal ideations. Four patients (7.7%) treated with *Paxil Tablets*, 8 patients (20%) in the imipramine group, and 4 patients (12.1%) in the placebo group dropped out due to an adverse event. Adverse events related to the nervous system and leading to withdrawal occurred in 3 patients in the *Paxil Tablets* group (for emotional lability [e.g., suicidal ideation/gestures]), 3 patients in the imipramine group (1 for emotional lability [e.g., suicidal ideation/gestures], 1 for neurosis, and 1 for convulsion), and 1 patient in the placebo group (for emotional lability [e.g., suicidal ideation/gestures], hostility, and manic reaction). All other events leading to withdrawal occurred in ≤1 patient in any group.

Table 1. Adverse Events Occurring in ≥5% of *Paxil Tablets* and Imipramine Groups and Twice the Rate of Placebo (approximately 4 months of exposure for each group)⁽¹¹⁾

Adverse Event	<i>Paxil Tablets</i>	Imipramine	Placebo
	N = 52 n (%)	N = 40 n (%)	N = 33 n (%)
Abdominal pain	6 (11.5%)	4 (10%)	1 (3%)
Weight gain	4 (7.7%)	1 (2.5%)	0 (0%)
Emotional lability (e.g., suicidal ideation/gestures)	4 (7.7%)	1 (2.5%)	1 (3%)
Insomnia	4 (7.7%)	3 (7.5%)	1 (3%)
Tremor	3 (5.8%)	0 (0%)	0 (0%)
Tachycardia	1 (1.9%)	2 (5%)	0 (0%)
Dry mouth	1 (1.9%)	3 (7.5%)	0 (0%)
Myalgia	1 (1.9%)	3 (7.5%)	0 (0%)
Dyspepsia	0 (0%)	2 (5%)	0 (0%)

Combing the safety data for the acute phase and continuation phases of Study 329 showed that emotional lability (e.g., suicidal ideation/gestures) was the only serious adverse event reported in the *Paxil Tablets* group at an incidence ≥5% and twice the rate of placebo.⁽¹¹⁾ Serious adverse events of emotional lability (e.g., suicidal ideation/gestures) were reported in 5 patients treated with *Paxil Tablets* (5.4%) during the acute phase and 3 patients treated with *Paxil Tablets* (5.8%) in the continuation phase; of these, 1 patient had a serious adverse event of emotional lability (e.g., suicidal ideation/gestures) in both phases.

Study 377: In a 12-week, double blind, placebo-controlled, multi-center study, the safety and efficacy of *Paxil Tablets* (20 to 40 mg daily) was evaluated in the treatment of adolescents (N = 286; 13 to 18 years) with MDD based on DSM-IV criteria.^(2,12) Treatment with *Paxil Tablets* did not show a statistically significant improvement in either of the primary endpoints as compared to placebo for the LOCF dataset at the end of 12 weeks: the proportion of patients with a ≥50% reduction in the Montgomery Asberg Depression Rating Scale (MADRS; $P = 0.702$) and a change between baseline and endpoint in the K-SADS-L ($P = 0.616$). Secondary endpoints also showed no statistically significant improvement of *Paxil Tablets* treated patients over the placebo group: change in MADRS total score ($P = 0.520$), change in Clinical Global Improvement Severity of Illness (CGI-S; $P = 0.847$), CGI-I score ($P = 0.283$), CGI-I

responders ($P = 0.045$), change in Beck Depression Inventory (BDI; $P = 0.734$), and change in Mood and Feelings Questionnaire (MFQ; $P = 0.681$). Withdrawals due to adverse events occurred in 11.8% of the *Paxil Tablets* treated group compared to 7.1% of the placebo group (not statistically significant). Similar proportion of patients from both treatment groups experienced adverse events (*Paxil Tablets* 66% and placebo 59%). The most common adverse event ($\geq 5\%$ and twice the rate of placebo) during therapy with *Paxil Tablets* as compared to placebo was decreased appetite (7.7% vs. 3.2%). A post-hoc analysis of the incidence of suicide related events (suicide threats, suicide gestures, suicide ideation, suicide attempts) showed that there were 8 patients in the *Paxil Tablets* treated group (4.4%; 4 patients ≤ 16 years and 4 patients >16 years) and 2 patients in the placebo group (2.1%; ≤ 16 years) who experienced a suicide-related adverse event ($P = 0.5$; Odds ratio [OR] = 2.15). Of the events that involved a suicide attempt, 3 occurred in *Paxil Tablets* treated patients (1.7%; 1 patient ≤ 16 years and 2 patients >16 years) and 2 were reported in the placebo group (2.1%; 2 patients ≤ 16 years; $P = 1$; OR = 0.78).

Study 701: In a 8-week, randomized, double blind, placebo-controlled, multicenter study, the safety and efficacy of *Paxil Tablets* (10 to 50 mg daily) was evaluated in the treatment of children (7 to 11 years) and adolescents (12 to 17 years) diagnosed with MDD based on DSM-IV criteria ($N = 203$).^(3,13) Treatment with *Paxil Tablets* did not show a statistically significant improvement in the primary endpoint as compared to placebo for the LOCF dataset at the end of 8 weeks: the change from baseline in Children's Depression Rating Scale-Revised (CDRS-R) total score (-22.6 for *Paxil Tablets* vs. -23.4 for placebo; $P = 0.684$). Secondary endpoints also showed no statistically significant improvement of *Paxil Tablets* treated patients over the placebo group: change from baseline in the CGI-S item score ($P = 0.780$ for children and $P = 0.485$ for adolescents), the proportion of responders based on the CGI-I item ($P = 0.563$; where response was defined as a score of 1 [very much improved] or 2 [much improved]); and the change from baseline on the Global Assessment of Functioning (GAF) scale ($P = 0.456$). In total, 8.9% (9/101) of *Paxil Tablets* patients and 2.0% (2/102) of placebo patients in the intent-to-treat (ITT) population withdrew during the treatment phase due to an adverse event. The only adverse events leading to withdrawal that occurred in more than 1 patient in the same treatment group were depression (experienced by 4 patients in the *Paxil Tablets* group) and emotional lability (experienced by 2 patients in the placebo group and 1 patient in the *Paxil Tablets* group). More children than adolescents withdrew due to adverse events in the *Paxil Tablets* group. The most common treatment phase adverse events ($\geq 5\%$ and at least twice the rate of placebo) during therapy with *Paxil Tablets* as compared to placebo were increased coughing (5.9% vs. 2.9%), dyspepsia (5.9% vs. 2.9%), vomiting (5.9% vs. 2.0%), and dizziness (5.0% vs. 1.0%).

Meta-analysis of the 3 studies: A meta-analysis was conducted on the 3 studies discussed above in pediatric patients diagnosed with MDD.⁽¹⁴⁾ There was no significant difference between *Paxil Tablets* and placebo on the primary efficacy endpoints in any of the 3 studies. The response rate, based on pooled CGI-I data, was significantly greater for the patients treated with *Paxil Tablets* in the total population [62.5% vs. 50.7%; OR 1.51 (95% CI: 1.09, 2.09); $P=0.012$]. However, this result was driven primarily by the 15 to 18 year-old group. There was no difference between *Paxil Tablets* and placebo in any subgroups comprised of only patients <15 years of age with no evidence of greater remission in patients <15 years of age or the overall population. Children receiving *Paxil Tablets* had greater drop-out rates due to adverse events than adolescents receiving *Paxil Tablets*.⁽¹⁵⁾ Insomnia (5.9% vs. 0%) and vomiting (5.9% vs. 2.1%) were the most common adverse events in children taking *Paxil Tablets* while somnolence (13.1% vs. 5.9%), tremor (5.5% vs. 1.3%), and decreased appetite (7.0% vs. 3.4%) were most common in adolescents taking *Paxil Tablets* as compared to placebo, respectively. Serious emotional lability, which may include suicidal thinking and/or behaviors, was more common in adolescents treated with *Paxil Tablets*.

Obsessive Compulsive Disorder

Study 453: The safety and efficacy of *Paxil Tablets* (10 to 60 mg daily) was evaluated for the treatment of OCD in children (8 to 11 years; $n = 167$) and adolescents (12 to 17 years; $n = 168$).^(4,16) Following 16 weeks of open-label therapy of *Paxil Tablets*, responders, defined as a $\geq 25\%$ decrease in the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) score and a CGI-I score of 1 or 2, were randomized to receive *Paxil Tablets* ($n = 95$) or placebo ($n = 98$) in a double-blind 16-week extension. During the first 16-week phase of the study, 68.7% of patients responded after treatment with *Paxil Tablets*. After

the 16-week, double-blind, placebo controlled phase, the primary endpoint of relapse rates (defined as any worsening of CGI-I score by 1 point for two consecutive visits or a worsening of 2 or more points at any single visit, or a CGI-I score of ≥ 5) was 34.7% for *Paxil Tablets* and 43.9% for placebo ($P = 0.136$). Time to relapse also did not show a difference compared to placebo ($P = 0.104$). Mean change in CY-BOCS score was +3.6 in the *Paxil Tablets* group compared to +6.9 in the placebo group ($P = 0.008$). The *Paxil Tablets* group (28.9%) had more patients with $\geq 25\%$ decrease in CY-BOCS score as compared to the placebo group (14.4%; $P = 0.023$). Suicide attempt/ideation was reported in several patients. Summaries by age group suggest behavioral activation/hyperactivity type adverse events (agitation, hostility, hyperkinesia, manic reaction, concentration impairment, tremor, myoclonus) were more likely to occur in the younger age group (<12 years). The most common treatment phase adverse events ($\geq 5\%$ and twice the rate of placebo) during therapy with *Paxil Tablets* as compared to placebo were hostility (6.3% vs. 0%) and dysmenorrhea (6.3% vs. 0%).

Study 704: In a 10-week, double blind, placebo-controlled, multi-center study, the safety and efficacy of *Paxil Tablets* (10 to 50 mg daily) was evaluated in the treatment of children (7 to 11 years; $n = 115$) and adolescents (12 to 17 years; $n = 88$) diagnosed with OCD based on DSM-IV criteria.^(5,17) The change in CY-BOCS scores (primary endpoint) showed a statistically significant difference in the *Paxil Tablets* group as compared to placebo (-8.8 vs. -5.3; $P = 0.002$; LOCF). Secondary endpoints with *Paxil Tablets* as compared to placebo, respectively, were: the proportion of responders based on BY-BOCS (64.9% vs. 41.2%; $P = 0.002$; responders defined as $\geq 25\%$ reduction), the proportion of responders based on the CGI-I item (46.9% vs. 33.3%; $P = 0.081$; responders defined as a score of 1 [very much improved] or 2 [much improved]), change from baseline in CGI-S item score (-1.3 vs. -1.1; $P = 0.251$), and change from baseline in GAF (8.9 vs. 7.0; $P = 0.247$). The most common treatment phase adverse events ($\geq 5\%$ and twice the rate of placebo) during therapy with *Paxil Tablets* as compared to placebo were hyperkinesia (12.2% vs. 5.7%), trauma (10.2% vs. 2.9%), decreased appetite (9.2% vs. 1.0%), hostility (9.2% vs. 1.0%), diarrhea (8.2% vs. 1.9%), asthenia (8.2% vs. 1.0%), dysmenorrhea (6.7% vs. 2.4%), vomiting (6.1% vs. 1.9%), agitation (5.1% vs. 1.9%), neurosis (5.1% vs. 1.0%), and pain (5.1% vs. 2.9%). Abdominal pain (22.4% vs. 10.0%), hyperkinesia (17.2% vs. 5.0%), and insomnia and hostility (each 12.1% vs. 5.0%) were reported more frequently in children than in adolescent patients, respectively. Emotional lability (suicidal thoughts), which also led to withdrawal from the treatment phase, occurred in 1 patient in the *Paxil Tablets* group.

Social Anxiety Disorder

Study 676: In a 16-week, double blind, placebo-controlled, multi-center study, the safety and efficacy of *Paxil Tablets* (10 to 50 mg daily) was evaluated in the treatment of children (8 to 11 years; $n = 91$) and adolescents (12 to 17 years; $n = 228$) diagnosed with social anxiety disorder (SAD) based on DSM-IV criteria.^(6,18) The proportion of responders based on the CGI-I item (defined as a score of 1 [very much improved] or 2 [much improved]; primary endpoint) showed a statistically significant difference in the *Paxil Tablets* group as compared to placebo (77.6% vs. 38.3%; OR 7.02; 95% CI: 4.07, 12.11; $P < 0.001$; LOCF). Secondary endpoints with *Paxil Tablets* as compared to placebo, respectively, were: mean change from baseline in CGI-S item score (-2.0 vs. -1.0; $P < 0.001$), change from baseline in Liebowitz Social Anxiety Scale for Children and Adolescents (LSAS-CA) total score (-48.01 vs. -24.25; $P < 0.001$), change from baseline in Kutcher Generalized Social Anxiety Disorder Scale for Adolescents (K-GSADS-A) total score (-42.94 vs. -21.08; $P < 0.001$), change from baseline GAF (17.11 vs. 8.37; $P < 0.001$). Adverse events leading to withdrawal occurred in 5.5% of patients receiving *Paxil Tablets* and 1.3% of patients receiving placebo. Manic reaction was the only adverse event leading to withdrawal that occurred in >1 patient in the *Paxil Tablets* group. The most common treatment phase adverse events overall ($\geq 5\%$ and twice the rate of placebo) during therapy with *Paxil Tablets* as compared to placebo were insomnia (14.1% vs. 5.8%), decreased appetite (8.0% vs. 3.2%), and vomiting (6.7% vs. 1.9%). Treatment phase adverse events in children ($\geq 5\%$ and twice the rate of placebo) during therapy with *Paxil Tablets* as compared to placebo were respiratory disorder (15.2% vs. 6.7%), nervousness (15.2% vs. 4.4%), rash (10.9% vs. 4.4%), otitis media (10.9% vs. 2.2%), urinary incontinence (10.9% vs. 0%), hyperkinesia (8.7% vs. 0%), asthenia (6.5% vs. 2.2%), hostility (6.5% vs. 0%), and conjunctivitis (6.5% vs. 0%). Treatment phase adverse events in adolescents ($\geq 5\%$ and twice the rate of placebo) during therapy with *Paxil Tablets* as

compared to placebo were insomnia (14.5% vs. 5.4%), somnolence (14.5% vs. 7.2%), dyspepsia (8.5% vs. 3.6%), decreased appetite (8.5% vs. 2.7%), and vomiting (6.8% vs. 0.9%).

Analyses of Events Possibly Related to Suicidal Behavior

In the GSK pediatric trials, which included more than 1100 patients (aged 7 to 18 years) treated with *Paxil Tablets*, no patient committed suicide.^(19,20,21,22) Post-hoc, retrospective, statistical analyses of the placebo-controlled portions of 6 pooled GSK pediatric studies were conducted to evaluate adverse events possibly related to suicidal behavior. 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 was a blinded database search of any and all patients who presented with 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). The use of different analytic methods may produce different results.

A difference was seen between *Paxil Tablets* and placebo in suicidal thinking and suicide attempts (Table 2).⁽²¹⁾ There were 2 treatment period analyses (on therapy and on therapy plus 30-day follow-up). For both of these treatment analyses, evaluation of the incidence of these events by specific psychiatric disorder shows that the majority of events occurred in patients with MDD.

Table 2. Incidence of Events Possibly Related to Suicidal Behavior in Controlled Pediatric Studies⁽²¹⁾

Indication	On Therapy Only (Treatment Phase + Taper Phase) % (n/N)			On Therapy Plus 30-day Follow-Up (Treatment Phase + Taper Phase + Follow-Up Phase) % (n/N)		
	<i>Paxil Tablets</i>	Placebo	<i>P</i> -value	<i>Paxil Tablets</i>	Placebo	<i>P</i> -value
Overall	2.4% (18/738)	1.1% (7/647)	0.07	3.4% (25/738)	1.2% (8/647)	0.01
Major Depressive Disorder (MDD)	3.7% (14/378)	2.5% (7/285)	0.5	5.3% (20/378)	2.8% (8/285)	0.12
Obsessive-Compulsive Disorder* (OCD)	0.5% (1/195)	0% (0/205)	0.49	0.5% (1/195)	0% (0/205)	0.49
Social Anxiety Disorder*	1.8% (3/165)	0% (0/157)	0.25	2.4% (4/165)	0% (0/157)	0.12

*OCD and Social Anxiety Disorder studies excluded patients with co-morbid MDD
n = number of patients reporting event
N = total number of patients in treatment arm

A subset of patients from the 3 pediatric MDD studies defined as having no suicidal ideation at study entry were included in an analysis examining “emergent suicidal ideation” based on the individual rating scale suicide items of the HAM-D, MADRS, and CDRS-R scales.⁽²³⁾ In this analysis, “emergent suicidal ideation” was defined by rating scale increases of HAM-D item 3 from 0 at baseline to ≥ 1 or from 1 at baseline to ≥ 2 , MADRS item 10 from 0 or 1 at baseline to ≥ 2 , or CDRS-R item 13 from 1 or 2 at baseline to ≥ 3 at any time during the controlled phase of the trial (on therapy) (Table 3). Results from this analysis demonstrated that there were no statistically significant differences between the *Paxil Tablets* and placebo groups in the number of patients with treatment-emergent suicidal ideation. This was the case with all 3 studies combined and when each study was analyzed separately. Moreover, the analysis showed no potential safety signal with regard to “emergent suicidal ideation” measured by these scales.

Table 3. Analysis of Emergent Suicidal Ideation in the Pediatric Depression Controlled Trials⁽²³⁾

Major Depressive Disorder Studies	<i>Paxil Tablets</i> % (n/N)	Placebo % (n/N)	Odds Ratio	95% CI	P-value
All 3 Depression Studies	23.7% (54/228)	23.3% (41/176)	1.02	0.64, 1.63	1.000
Study 329	34.8% (23/66)	32.7% (18/55)	1.10	0.52, 2.34	0.849
Study 377	19.5% (16/82)	24.4% (11/45)	0.75	0.31, 1.79	0.507
Study 701	18.8% (15/80)	15.8% (12/76)	1.23	0.53, 2.83	0.676

n = number of patients with “emergent suicidal ideation” as defined above
N = total number of patients without baseline suicidal ideation in treatment arm

A blinded expert panel review of suicide-related events (suicide threat, suicide gesture, suicide ideation, or suicide attempt) occurring during the placebo-controlled portions of 5 randomized, double-blind trials (3 MDD, 1 OCD, and 1 social anxiety disorder; from 8 to 32 weeks) in children and adolescents (N=1,191) was conducted to compare the incidence rates between *Paxil Tablets* (n=642; 10 to 50 mg/day) and placebo (n=549).⁽²⁴⁾ No pediatric patient taking *Paxil Tablets* committed suicide. Suicide-related events occurred more often in the *Paxil Tablets* group (22/642; 3.4%) compared to placebo (5/549; 0.9%; OR 3.86; 95% CI: 1.45, 10.26; $P = 0.003$). All of these events occurred in the adolescent group (12 to 18 years), except for a suicide gesture made by one 10 year old patient treated with *Paxil Tablets*. All attempted suicides occurred in patients diagnosed with MDD.

A matched case-control study in children and adolescents (6 to 18 years) compared the risk of suicide attempts and completed suicides after inpatient treatment with any antidepressant medication for a depressive disorder.⁽²⁵⁾ Children/adolescents treated with paroxetine did not have a significantly increased risk of suicide attempts (OR 1.36; 95% CI: 0.8, 2.3; $P = 0.27$) compared to patients with no antidepressant treatment. For all antidepressant treatment (any SSRI, other antidepressant agents including tricyclic antidepressants), suicide attempts (OR 1.52; 95% CI: 1.12, 2.07; $P = 0.007$ [263 cases and 1241 controls]) and completed suicides (OR 15.62; 95% CI: 1.65, ∞; $P = 0.002$ [8 cases and 39 controls]) were significantly higher in children/adolescents treated with antidepressants compared to no antidepressant treatment. The majority of cases were >12 years, with 13 suicide attempts and no completed suicides in children ≤12 years.

A cohort study of all British Columbia residents 10–18 years of age with a diagnosis of depression who initiated an antidepressant between January 1, 1997 and December 31, 2005 was conducted to assess the risk of suicide attempts and suicides after initiation of individual antidepressant agents.⁽²⁶⁾ The study included a total of 20,906 children and adolescents initiated on any antidepressant. Paroxetine was the most common antidepressant (25%, n = 5221). Patients treated with paroxetine had a mean age of 15 years, 62% were female, and 14.3% were on at least 1 additional psychiatric medication. A total of 16,774 patients had no antidepressant use in the past 3 years and were used in the treatment-naive analysis. During the first year of antidepressant use, 268 patients overall attempted or completed suicide (27.0 suicidal acts/1000 person-years; 95% CI, 23.9–30.5) with 43 attempts classified as violent (4.3 violent suicidal acts/1000 person-years; 95% CI, 3.1–5.8). Most events occurred within the first 6 months after initiation. Violent suicide acts were described as hangings, gunshot/explosions, jumping/lying in front of a moving objects, stabbing/blunt traumas, vehicle collisions, electrocutions, and self-immolations. Seventy-one patients treated with paroxetine attempted suicide (29.38 suicidal acts/1000 person-years, 95% CI 22.94–37.05) and 17 of those patients attempted a violent suicide (6.98 violent suicidal acts/1000 person-years; 95% CI, 4.06–11.17). In the high dimension propensity score adjusted analysis of all patients and treatment naive patients, the rate ratio for suicidal acts with paroxetine compared to fluoxetine

(SSRI reference group) was 0.88 (95% CI, 0.57–1.35) and 0.80 (95% CI, 0.47–1.37), respectively. The same adjusted analysis for violent suicidal acts demonstrated a rate ratio of 3.25 (95% CI, 0.89–11.88) in all patients and 2.19 (95% CI, 0.57–8.43) in treatment naive patients using paroxetine compared with fluoxetine. A clinically meaningful variation in the risk of all suicidal acts according to individual antidepressant agent or class was not observed.

A retrospective, observational, cohort study investigated whether the risk of reported suicidal thinking and behavior was similar between adults and children with the use of SSRI and non-SSRI antidepressants and with the use of paroxetine and other SSRI antidepressants.⁽²⁰⁾ A total of 158,530 patients (≥ 10 years; treated for MDD or an anxiety disorder) were identified using the United Kingdom (UK) General Practice Research Database (GPRD) between 1988 and 2003. After adjusting for patient history, there were no statistically significant differences between SSRI and non-SSRI users (Hazard Ratio [HR] 0.96; 95% CI: 0.85, 1.08) or between users of paroxetine and other SSRIs 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 analyses, after adjusting for patient history, 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 the use of all other SSRIs (OR 1.39; 95% CI: 0.89, 2.16).

A meta-analysis of data derived from 24 pediatric trials (N = 4582) of 9 antidepressant drugs was undertaken to investigate the relationship between suicidality (suicidal ideation and behavior) and antidepressants in pediatric patients with MDD (n = 16), OCD (n = 4), GAD (n = 2), ADHD (n = 1), and social anxiety disorder (n = 1).⁽²⁷⁾ There were no completed suicides in any of the studies. The overall suicidality risk ratio (RR) was 1.95 (95% CI: 1.28, 2.98). SSRIs as a group were evaluated across MDD studies and found to have a suicidality RR of 1.66 (95% CI: 1.02, 2.68). Eight other studies had an RR ≥ 2 : paroxetine (n = 4), fluvoxamine (n = 1), sertraline (n = 1), and venlafaxine (n = 2). The suicidality RR for paroxetine across MDD trials was 2.15 (95% CI: 0.71, 6.52) and across all trials was 2.65 (95% CI: 1.00, 7.02). The risk difference (RD) analysis estimated the absolute increase in the risk of suicidality due to treatment. The overall RD for the primary outcome (suicidal behavior or ideation) and secondary outcome (possible suicidal behavior or ideation) were 0.01 (95% CI: 0.01, 0.02) and 0.02 (95% CI: 0.01, 0.03), respectively. The meta-analysis of the suicide item scores from 17 trials (using 1 of the 3 following scales: CDRS-R, HAM-D, or MADRS) did not produce a signal for excess suicidality for drug-treatment. The worsening of suicidality RR was 0.92 (95% CI: 0.76, 1.11) and emergence of suicidality RR was 0.93 (95% CI: 0.75, 1.15).

A systematic review of 8 observational studies including more than 200,000 patients assessed the overall risk of completed or attempted suicide in patients with moderate or severe depression exposed to SSRIs compared with those not exposed to antidepressants.⁽²⁸⁾ Exposure to SSRIs significantly increased the risk of suicidality among adolescents (OR 1.92, 95% CI 1.51–2.44). Two studies provided data that allowed analysis of the risk of completed or attempted suicide associated with individual antidepressants. This analysis found that among adolescents, exposure to paroxetine (OR 1.77, 95% CI 1.05–2.99) and venlafaxine (OR 2.43, 95% CI 1.47–4.02) was associated with significantly greater risk of completed or attempted suicide.

Pooled Retrospective Safety Analyses

Several retrospective analyses combined adverse event data from up to 5 acute (up to 16 weeks), randomized, multicenter, double-blind, placebo-controlled trials (N = 1,176) in order to evaluate the safety of *Paxil Tablets* (n = 633; 10 to 50 mg/day) in children (7 to 11 years) and adolescents (12 to 18 years) with MDD, OCD, or social anxiety disorder.^(29,30) Adverse events meeting the criteria, $\geq 2\%$ for *Paxil Tablets* and at least twice that for placebo, were: decreased appetite (7.4% vs. 2.9%), tremor (3.8% vs. 0.6%), hyperkinesia (3.5% vs. 1.5%), hostility (3.3% vs. 0.6%), emotional lability (3.2% vs. 1.5%; includes suicidal ideation/attempts/gestures/risk/self-injurious behavior/mood fluctuations and lability of mood), agitation (2.5% vs. 0.7%), and sweating (2.4% vs. 0.6%). There were no completed suicides

in any *Paxil Tablets* pediatric studies. This overall profile of adverse events is generally similar to that reported in the adult studies, with the exception of hyperkinesia, hostility, and emotional lability (includes suicidal ideation/attempts/gestures/risk/self-injurious behavior/mood fluctuations and lability of mood). A total of 53/633 (8.4%) patients treated with *Paxil Tablets* and 19/543 (3.5%) on placebo discontinued treatment due to adverse events. Common discontinuation AEs (incidence $\geq 2\%$ for *Paxil Tablets* and at least twice that for placebo) were nausea (6.2% vs. 2.1%), dizziness (6.2% vs. 0.7%), nervousness (3.6% vs. 1%), abdominal pain (3.3% vs. 1%), and emotional lability (2.3% vs. 0.3%; crying, mood fluctuations, self-harm, suicidal thoughts, and attempted suicide).⁽³¹⁾ Discontinuation AEs of suicidal ideation or suicide attempt occurred in four (1.3%) *Paxil Tablets*-treated patients and one (0.3%) placebo-treated patient. The overall incidence of bleeding-related adverse events (BRAEs) occurred with a higher frequency in the *Paxil Tablets* group compared to the placebo group (3.32% and 0.92%, respectively), with epistaxis as the most frequent BRAE in *Paxil Tablets*-treated pediatric patients (1.74% vs. 0.37% for placebo).⁽³²⁾ One serious BRAE (peptic ulcer hemorrhage) occurred in a *Paxil Tablets*-treated patient who had a history of bleeding ulcer. Concomitant use of medications which can impair hemostasis (e.g., non-steroidal anti-inflammatory drug [NSAID]) confounded the interpretation of these data. Of the *Paxil Tablets*-treated patients with a BRAE, 47.6% were taking a concomitant NSAID compared to 20% of placebo-treated patients.

Electrocardiographic Analysis

A retrospective analysis of 1451 electrocardiograms (ECGs) was conducted to evaluate the cardiovascular effects of *Paxil Tablets* (10 to 50 mg daily) in pediatric patients (7 to 18 years) with MDD or OCD during 3 randomized, double-blind, placebo-controlled and imipramine-controlled trials (N = 449; *Paxil Tablets* n = 200; imipramine n = 42; placebo n = 207).⁽³³⁾ ECGs were analyzed for heart rate and corrected QT interval (using Bazett's formula [QTcB] and Fridericia's formula [QTcF]) at baseline and while being treated. Analysis of PR, R-R, and QRS intervals, as well as, maximum change from baseline in QTcB and QTcF intervals was conducted. Imipramine significantly lengthened the QTcB-interval values. Overall, there was no significant difference between *Paxil Tablets* and placebo across all QTc indices or other ECG parameters. These data suggests that *Paxil Tablets* is not associated with QT-interval prolongation in healthy pediatric patients.

Pharmacokinetics

In a steady state pharmacokinetics study of *Paxil Tablets* in children (7 to 11 years) and adolescents (12 to 17 years) with MDD or OCD, the steady-state maximum plasma concentration of *Paxil Tablets* (C_{max}) and area under the curve (AUC[0-24]) at each dose level (10, 20, and 30 mg daily) was higher in children than in adolescents, and clearance (CL/F) was lower in children compared to adolescents.^(34,35) C_{max} and AUC(0-24) increased disproportionately with dose (from 10 mg to 30 mg daily) but became less variable mirroring the behavior of *Paxil Tablets* in the adult population. Values for the median time it takes *Paxil Tablets* to reach C_{max} (T_{max} = 3 to 5 hr) suggested no difference in absorption rate between children and adolescents. The results do not warrant a weight-based dosing regimen in the pediatric population. In another study, increased dose (weight normalized) was also associated with reduced CL/F (the typical 40 kg subject receiving 10 mg first-dose CL/F = 5.4 L/hr/kg and steady-state CL/F = 0.9 L/hr/kg).⁽³⁶⁾ Typical V_d/F was 48 L/kg. The metabolism of paroxetine in children and adolescents appears to be time dependent and saturable. While overall the paroxetine CL/F in children and adolescents are similar to published data in adults, there is high inter-subject variability and paroxetine exposure varies greatly within this population. Findling et al conducted an 8-week, open-label study to assess the pharmacokinetics and safety of *Paxil Tablets* in 30 children and adolescents (5 to 17 years) with MDD.⁽³⁷⁾ Fifteen patients received *Paxil Tablets* 10 mg daily for 8 weeks, and the average paroxetine concentration was 12.9 ng/mL (standard deviation [SD] 8.4) at week 4 and 7.2 ng/mL (SD 7.5) at week 8. Eight patients that had their *Paxil Tablets* dose increased to 20 mg daily at week 4, and the average paroxetine concentrations were 10 ng/mL (SD 9.7) and 48.9 ng/mL (SD 47.5) at weeks 4 and 8, respectively.

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.)

Some information contained in this response is outside the approved Prescribing Information. This product is not approved for the use described. This response is not intended to offer recommendations for administering this product in a manner inconsistent with its approved labeling.

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.

For a complete bibliography of publications/presentations relating to the use of *Paxil Tablets* in pediatric patients, please visit the company website, www.gsk.com. This website also includes the pediatric clinical trial data for *Paxil Tablets*, clinical study reports conducted by GSK (synopses and full reports), and this Medical Information letter.

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