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September 11, 2001

Redacted

Dear Ms Redacted

Your Pharmaceutical Consultant, Brittney Powell, forwarded your request for information regarding the use of Paxil® (paroxetine hydrochloride) for the treatment of depression, obsessive compulsive disorder (OCD), panic disorder, social anxiety disorder (social phobia) or generalized anxiety disorder (GAD) in children and/or adolescents.

SUMMARY

- *Paxil* is not FDA-approved for use in children or adolescents; therefore, we may not offer any recommendations regarding the use of *Paxil* in these patients.

- A search of the Medical Information Department's published literature database and MEDLINE identified several studies and case reviews discussing the use of *Paxil* in children or adolescents for the treatment of depression, OCD, panic disorder or social anxiety disorder. In the identified publications patient ages ranged from 5 to 18 years.

- A double-blind, placebo-controlled study by Keller et al evaluated treatment of *Paxil* and imipramine in adolescents with depression. In this study *Paxil* was superior to placebo by several assessment methods, including Hamilton Depression Rating Scale (HAM-D) total score ≤ 8, and to be tolerated better than treatment with imipramine.

- Two additional small open-label studies and one retrospective study support the findings of the above study. However, further evaluation is needed to clearly establish the efficacy and safety of *Paxil* in the treatment of adolescents with depression.

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- The use of *Paxil* in the treatment of children and adolescents with OCD has been evaluated in several open-label studies. Overall, treatment with *Paxil* showed improvement in symptoms, however, conclusions regarding the efficacy and safety of *Paxil* for the treatment of OCD in this patient population awaits adequately designed, double blind, placebo-controlled trials.

- Published data regarding the use of *Paxil* in children or adolescents for the treatment of panic disorder and social anxiety disorder are limited to a few case reports. The reports are favorable, however, well-designed studies in children and adolescents with these disorders are needed. No studies or case reports were identified that discussed the use of *Paxil* for GAD.

- Findling et al conducted a pharmacokinetic study in children and adolescents with depression demonstrated many similarities between adults and children in terms of pharmacokinetics. However, the half-life was considerably shorter in the younger patients compared to adults suggesting more rapid clearance.

Depression

Keller et al (2001) conducted an 8-week, double-blind, placebo-controlled, multicenter trial comparing the safety and efficacy of *Paxil* and imipramine in the treatment of adolescents with major depression. A total of 275 adolescents (12 to 18 years), who met DSM-IV criteria for major depression, were randomized to receive *Paxil* 20 mg/day (n = 93), imipramine 200 mg/day (dose titrated from 50 mg/day over a period of 3 weeks, n = 95), or placebo (n = 87). Patients were treated for a total of eight weeks and 190 patients completed the study. If no response was noted at week 4, treatment could be increased over the next two weeks to a maximum of 40 mg/day of *Paxil* or 300 mg/day of imipramine.

The primary efficacy parameters included the proportion of responders with a ≤ 50% reduction from baseline on the HAM-D or a final HAM-D score of ≤ 8 and the mean change from baseline in HAM-D total scores at endpoint. Secondary assessments included mean Clinical Global Impression Improvement (CGI-I) scores and the 9-item depression subscale of the Schedule for Affective Disorders and Schizophrenia for School-age Children – Lifetime version (K-SADS-L). In the depression-related parameters, *Paxil* was statistically superior to placebo at endpoint among four parameters: 1) response defined as HAM-D ≤ 8; 2) HAM-D depressed mood item; 3) K-SADS-L depressed mood item; and 4) CGI-I score of 1 (very much improved) or 2 (much improved).

Analysis of last observation carried forward (LOCF) at endpoint resulted in significant separation (p = 0.02) between the percentage of responders defined as HAM-D ≤ 8 among those treated with *Paxil* (63.3%) compared to placebo (46%). The percentage of responders in the imipramine group (50%) did not separate from placebo. Analysis of observed cases (OC) at endpoint resulted in significant separation (p = 0.02) between the

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percentage of responders among those treated with *Paxil* (76.1%) compared to placebo (57.6%). The percentage of patients treated with *Paxil* who had a CGI-I of 1 or 2 was 65.6% compared to 48.3% with placebo ($p = 0.02$). Premature withdrawal rates from the study due to adverse events were highest (40%) in the imipramine group ($p = 0.02$ versus placebo), compared to 28% and 20% in the *Paxil* and placebo groups ($p = 0.60$ versus placebo), respectively. Withdrawal from the study due to adverse events was (31.5%) in the imipramine group, compared to 9.7% and 6.9% in the *Paxil* and placebo groups, respectively. The most common adverse events during therapy with *Paxil* included headache, nausea, dizziness, dry mouth and somnolence. All of the events were reported in an incidence similar to placebo with the exception of somnolence, *Paxil* 17.2% vs. placebo 3.4%. In the imipramine treatment group, the most common adverse events included dizziness, dry mouth, headache, nausea and tachycardia.

Rey-Sánchez et al (1997) conducted an open-label study of *Paxil* in the treatment of major depression in children less than 14 years of age. Patients ($n = 45$, mean age 10.7), meeting DSM-III-R criteria for major depressive disorder, were treated with *Paxil* (initial dose 10 mg/day; mean final dose 16 mg/day) in an outpatient setting. Treatment was continued until the depressive episode was completely resolved. Disease severity was measured utilizing a 5-point Clinical Global Severity scale (CGS) at baseline, month 1, month 3 and at the end of treatment. Response was reported as the intensity of therapeutic response (ITR), a reflection of point change in CGS. At baseline, the mean CGS was 3.0 (range 2-4). At month 1, the mean CGS was 2.2 (range 1-4; mean ITR = 0.8) and at month 3 the mean CGS was 1.2 (range 0-3, mean ITR = 1.8). A complete remission of symptoms was reported in all patients at the end of treatment (mean duration 8.4 months). No patient experienced a worsening of symptoms. Patients were permitted to receive benzodiazepines during the study if needed; 16/45 (36%) patients were treated as such for insomnia or acute anxiety. Adverse events were reported in 4/45 (9.5%) of the patients (vomiting during the first four days of treatment, anxiety and nervousness, abdominal pain, abdominal cramps and nausea). These events were reported as mild to moderate with no patient withdrawals.

Masi et al (1997) reported improvement in four of seven patients (ages 14 to 18 years) with intellectual disability (IQ range 53 to 68) treated with *Paxil* (20 to 40 mg/day) for major depressive disorder. Adverse events included sedation, insomnia, nausea and dyspepsia. In a retrospective review, Rodriguez-Ramos et al (1996) reported findings in 25 adolescents, aged 13 to 17 years, treated with *Paxil* (10 to 40 mg/day) for either primary or secondary depression. Total remission was reported for 11/25 (44%) patients, improvement with residual symptoms in 8/25 (32%) patients, and no change in 4/25 (16%) patients. Common adverse events included asthenia, somnolence and nausea. Two patients withdrew from the treatment due to adverse events (dizziness with hypotension, anxiety).

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Obsessive Compulsive Disorder

Carpenter et al (2000) reported on the safety and efficacy of *Paxil* for the treatment of OCD in children (8 to 11 years; n = 167) and adolescents (12 to 17 years; n = 168). Following 16 weeks of open-label therapy of *Paxil* 10 to 60 mg/day, responders, defined as a ≥ 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* or placebo in a double-blind 16-week extension. The baseline mean CY-BOCS score was 26.3. During the first phase of the study, the mean CY-BOCS score was reduced by 13. Of those completing the first 16 weeks of the study, 86% met response criteria. After the double-blind phase, 28.9% in the *Paxil* group experienced a further decrease in CY-BOCS score compared to 14.4% in the placebo group (p = 0.023). Mean increase, or worsening, in CY-BOCS score was +3.6 in the *Paxil* group compared to +6.9 in the placebo group (p = 0.008). While relapse rates (defined as any worsening of CGI-I score for two consecutive visits or a worsening of 2 or more points at any single visit) were lower for *Paxil* (34.7%) compared to placebo (43.9%), the findings did not reach statistical significance (p = 0.136).

Adverse events leading to discontinuation were generally low; the most common events included hostility (2.7%), hyperkinesia (2.1%) and agitation (1.8%). Even though the incidence of adverse events was similar in children and adolescents, agitation (11.4% vs 3.6%), hyperkinesia (14.4% vs 8.3%), trauma (18.6% vs 8.3%), infection (12.0% vs 7.1%), manic reaction (4.2% vs 0.6%) and myoclonus (9.6% vs 4.8%) were reported more frequently in the younger age group.

Diler et al (2000) conducted a 12-week, open-label study to assess the safety and effectiveness of paroxetine in 47 pediatric patients with OCD (DSM-IV criteria) not previously treated for the condition. Of the enrolled patients (aged 9 to 15 years), 19 (40%) had one comorbid diagnosis, 8 (17%) had two comorbid diagnoses, 4 (9%) had three comorbid diagnoses and 16 (34%) had no comorbid diagnoses. The comorbid diagnoses were major depression (n = 14), social anxiety disorder (n = 10), Tourette's syndrome (n = 5), generalized anxiety disorder (n = 4), panic disorder (n = 4), stuttering (n = 4), conversion disorder (n = 4), attention-deficit hyperactivity disorder (n = 2), conduct disorder (n = 2), trichotillomania (n = 2), encopresis (n = 1), and night terror (n = 1). Patients started treatment with paroxetine 10 mg/day for one week and were increased to a fixed dose of paroxetine 20 mg/day for five weeks; for the following six weeks the treating psychiatrist could maintain or change the dosage based on efficacy or adverse events. During the study, the mean dose was paroxetine 20.7 mg/day. No additional medication was used. Efficacy was assessed at baseline, weeks 3, 6 and 12 by Maudsley Obsessive Compulsive Inventory (MOCI), Children's Depression Inventory (CDI), Clinical Global Impressions-Severity of illness (CGI-SI) scale and Spielberger's State-Trait Anxiety Inventory for Children (SAI-C and TAI-C). Adverse events were assessed by the Adverse Experience Scale and the CGI-Adverse Effects scale.

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At week 6, evaluation of 42 patients (five patients withdrew at week 6 due to noncompliance with study protocol) revealed significantly lower scores on the total MOCI, CDI, SAI-C, TAI-C and CGI-SI scale. These findings were sustained at study endpoing. At week 12, 61.9% (26) patients showed ≥ 50% improvement according to the MOCI. The mean reduction in the CGI-SI score was 56.8% ± 19.4%. The most commonly reported adverse events included sleepiness (23.4%), increase in anger (8.5%) and fatigue (8.5%). The percentage of patients with no adverse events increased from 34.5% at week 3 to 64.3% at week 12. No patient experienced adverse events severe enough to discontinue the drug.

Rosenberg et al (1999) conducted a 12-week, open-label trial of *Paxil* in 20 children (9 boys, 11 girls) ages 8 to 17 years with OCD (DSM-IV criteria). Twelve of the children had comorbid psychiatric conditions including anxiety disorders other than OCD (n = 3), eating disorders (n = 3), trichotillomania (n = 1), attention-deficit hyperactivity disorder (n = 1), dysthymia (n = 1), oppositional defiant disorder (n = 1) and tic-related/Tourette's disorder (n = 2). Response assessments were made at baseline and weeks 2, 4, 6, 8 and 12. Response was evaluated utilizing the CY-BOCS, the Children's Global Assessment Scale (CGAS) and the CGI scale. In addition, the severity of tics and anxiety was evaluated with the Yale Global Tic Severity Scale and the Hamilton Anxiety Rating Scale (HAM-A) at baseline and weeks 4, 8 and 12.

Paxil was initiated at 10 mg/day in all patients and could be increased in increments of 10 mg/day every two weeks up to a maximum of 60 mg/day (final mean dose 41 mg/day). Nineteen patients completed 12 weeks of treatment; the remaining patient was assessed at week 8 and was included in the analysis. A significant (p = 0.0001) reduction in CY-BOCS scores from baseline was noted at endpoint. Significant improvements in CGAS scores (p = 0.0001) and CGI scores (p = 0.0001) were also noted (Table 1).

Table 1: Treatment Response at Endpoint

	Baseline	Endpoint	p value*
CY-BOCS	30.55 ± 3.50	21.60 ± 6.83	0.0001
CGAS*	46.79 ± 7.34	57.47 ± 7.89	0.0001
CGI	5.63 ± 0.60	4.26 ± 1.04	0.0001

* increase scores indicates improvement

In general, OCD response did not appear to correlate with any comorbid disorders. The two patients with tics did not respond to treatment and one of these patients experienced a worsening of tics. Adverse events were rated every two weeks on the Adverse Experience Scale. Mild adverse events included hyperactivity/behavioral disinhibition (n = 6), headache (n = 5), insomnia (n = 3) gastrointestinal distress (n = 3), increased anxiety (n = 2), drowsiness (n = 1) and dry mouth (n = 1); severe treatment-emergent adverse events included suicidal ideation (n = 1) and increased tics (n = 1). The authors noted that they did not observe any hypomania or mania in these patients.

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Thomsen et al (1999) examined the addition of buspirone to existing selective serotonin reuptake inhibitor (SSRI) therapy in six adolescents with OCD. Of these patients, one 15-year-old male was treated with paroxetine. After three months of treatment with paroxetine 60 mg/day (starting dose or titration schedule not provided), there was a reduction of Y-BOCS score from 33 to 28. After approximately 6 weeks of combination therapy with paroxetine and buspirone 20 mg/day, his Y-BOCS score was 22. In addition, a decrease in the subject's obsessive-compulsive symptoms was noted. Specifically, a reduction in his evening rituals and less anxiety when trying to resist compulsions. The subject reported extreme tiredness after three weeks of combination therapy, but this dissipated after week 5.

Panic Disorder

Response to treatment with a number of different SSRIs, including *Paxil* was evaluated in an naturalistic, open-label study consisting of two phases: an acute treatment period consisting of six to eight weeks and follow-up phase lasting approximately six months (Renaud, 1999). Twelve patients, ages 7 to 17 years (mean age 16 years), with panic disorder (DSM-IV criteria) were included in the study, including eight patients with another comorbid anxiety disorder (generalized anxiety, separation anxiety, social phobia). Assessments were made utilizing a variety of anxiety scales, panic disorder scales, the CGI scale and the CGAS. The frequency of panic attacks was not noted.

Patients were treated with fluoxetine unless there was a previous unsuccessful trial with fluoxetine or the patient refused it. Two patients were treated with *Paxil* during the acute phase (20 or 60 mg/day) and three were treated with *Paxil* during the follow-up phase (10 to 30 mg/day). Because of the naturalistic nature of the study, eight patients, including one of the patients treated with *Paxil*, received a concomitant benzodiazepine (clonazepam or lorazepam).

At the end of the study (end of follow-up) significant improvement was noted in the mean CGI-Severity scores (baseline 4.4, endpoint 2.2, $p = 0.002$). The mean time to achieve a CGI-Improvement score of 1 or 2 (much or very much improved) was 10.5 weeks. Significant improvement was also noted with the C-GAS score (baseline 48.3, endpoint 74.3, $p < 0.001$). The two patients treated with *Paxil* throughout the study had improvements from baseline scores of 51 and 45 to final scores of 82 and 70, respectively. Adverse events were assessed with the Side Effects Form for Children and Adolescents. No significant differences were noted in adverse events from baseline to endpoint.

Social Anxiety Disorder

Mancini et al (1999) reported response to treatment with a serotonergic agent in a consecutive series of seven patients (ages 7 to 18 years) with generalized social anxiety disorder. Five of these patients were treated with *Paxil*; the remaining two patients were treated with sertraline or nefazodone. The initial dose of *Paxil* was in the range of 5 to 20

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mg/day. Over a few weeks, the dose was increased until there was a response or the dose was no longer tolerated. The maximum dose ranged from 5 to 80 mg/day. Initial response was seen between week 4 and week 9 of treatment. One adverse event was reported for each of the treatments: somnolence was reported with *Paxil*; diarrhea was reported with sertraline, and difficulty with visual accommodation was reported with nefazodone.

Pharmacokinetics

Findling et al (1999) conducted an 8-week, open study to assess the pharmacokinetics and safety of paroxetine in 30 adolescents (aged 5 to 17 years) with depression (DSM-IV criteria). In addition to DSM-IV criteria, younger patients needed a score of at least 40 on the Children's Depression Rating Scale (CRDS) and older subjects were required to have a HAM-D score ≥ 17. Patients were initiated on paroxetine 10 mg/day. After four weeks, the dose could be increased to 20 mg/day based on response. Following a single dose of paroxetine 10 mg, the mean Cmax, Tmax, half-life and area under the curve (AUC) were 5.5 ng/mL (SD 4.0), 5.7 ng/mL (SD 1.9), 11.1 hr (SD 5.2) and 0.09 mcg•hr/mL (SD 0.10), respectively. There were 15 subjects who received paroxetine 10 mg/day for eight weeks. For these patients, the average paroxetine concentration was 12.9 ng/mL (SD 8.4) at week 4 and 7.2 ng/mL (SD 7.5) at week 8. There were eight subjects that had their paroxetine dose increased to 20 mg/day at week 4. For these patients, the average paroxetine concentration was 10.0 ng/mL (SD 9.7) at week 4 and 48.9 ng/mL (SD 47.5) at week 8. Efficacy results in terms of HAM-D and CRDS were not provided.

Overall, adverse events were mild and transient; gastrointestinal events (e.g., nausea, abdominal cramps) were reported most commonly. The only adverse event that led to treatment discontinuation was hypomania and this occurred in two patients at a dose of 10 mg/day. There were no clinically significant changes in weight, blood pressure, pulse, electrocardiogram, serum chemistry and hematological studies noted.

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I appreciate your interest in *Paxil*. The citations noted may contain information on uses, doses, dosage forms, routes of administration or specific patient populations which are not described in the approved prescribing information for *Paxil*. GlaxoSmithKline makes no recommendations beyond those in the approved labeling and suggests that you review the enclosed prescribing information before initiating therapy. If you have further questions regarding our products, please contact the Medical Information Department at 800-366-8900.

Sincerely,

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Medical Information Department

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Enclosures: **Prescribing Information for *Paxil.*** PXL0

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