SEPTEMBER 10, 2003 GENERAL PHARMACEUTICALS

GSK SALES CONNECTION

SPECIAL FEATURE

Inside Front Cover: Augmentin XR Ad
Page One: Employee Referral Bonus Ad
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ACTION

Clean out your E-mail Field Servers 2

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GlaxoSmithKline

MEMO

MEDICAL INFORMATION DEPT.

September 08, 2003

To: Representatives with Paxil CR Selling Reponsibilities

From: Medical Information Department

Paxil CR Team (Christine Ketchie, Traci Lee, Nayahmka McGriff-Lee)

cc: Paxil CR Prod. Mgt.
B. Rossello
RVPS
TSMs
DSMs
MDMs

Subject: REVISED MEDICAL INFORMATION LETTER ON THE USE OF PAXIL IN PEDIATRIC PATIENTS

Specifics

We wanted to give you an update on the Paxil pediatric issue around suicide. The FDA is still reviewing our safety data for a possible increase in suicidal behavior in this population. However, clinical trial data regarding Paxil use in pediatric patients (specifically events possibly related to suicidal behavior) has been added to the Paxil/Paxil CR Medical Information pediatric letter. It includes some of the safety data submitted to the FDA.

This letter is for your informational purposes only. Although you should read the letter carefully, please do not discuss the contents with your customers. Instead, refer all questions/requests to Medical Information. The revised letter has been sent to the healthcare professionals (HCPs) who have asked for it since this issue arose in June. Therefore, if you already requested this data for one of your doctors, they have been sent the revised information.

When we hear back from the FDA with regards to their decisions on the Paxil labeling, we will let you know.

In the meantime, if you have questions regarding this data, please call the Customer Response Center (CRC): 888-825-5249.

Damage control — reps instructed to hold back info.

Does this refer to July 03 letter — if so, suggests no change in advice to Drs yet

RE: USE OF PAXIL CR™ OR PAXIL® IN PEDIATRIC PATIENTS

SUMMARY

- Paxil® (paroxetine HCl) and Paxil CR™ (paroxetine HCl) Controlled-Release are not approved by the US Food and Drug Administration (FDA) for use in patients less than 18 years of age (children or adolescents); therefore, no recommendations can be made regarding use of *Paxil* or *Paxil CR* in these patients.

- A search of the published literature identified several studies and case reviews discussing the use of *Paxil* in children or adolescents for the treatment of major depressive disorder (MDD), obsessive compulsive disorder (OCD), social anxiety disorder, or panic disorder. In the identified data, patient ages ranged from 5 to 18 years and the dosage of *Paxil* ranged 5 to 80 mg/day. No studies or case reports were identified that discussed the use of *Paxil* for the treatment of generalized anxiety disorder (GAD) or posttraumatic stress disorder (PTSD) in children or adolescents. No studies were identified examining *Paxil CR* in pediatric patients.

- From an efficacy standpoint, trials in pediatric patients have shown *Paxil* to be statistically superior to placebo in the treatment of OCD and social anxiety disorder. The studies did not show a benefit for the treatment of MDD in children or adolescents under 18 years of age. Conclusions regarding the efficacy and safety of *Paxil* and *Paxil CR* in children and adolescents for the treatment of panic disorder, GAD, and PTSD await further study.

- The FDA posted a Talk Paper on their website on June 19, 2003 acknowledging that they are reviewing the GlaxoSmithKline *Paxil* pediatric trial database (1). The FDA is evaluating the *Paxil* safety data for a possible increased risk of suicidal thinking and suicide attempts in children and adolescents. Although the review is not complete, the FDA currently recommends that *Paxil* not be used in children or adolescents with depression. As in adults, for children and adolescents taking *Paxil*, it is important that *Paxil* not be abruptly discontinued. Upon completion of the review, additional information will be available.

- With respect to adults, the FDA has acknowledged that there is no evidence that *Paxil* is associated with an increased risk of suicidal thinking or behavior in adults.

- In the GlaxoSmithKline pediatric trials, which included more than 1,100 patients (aged 7 to 18 years) treated with *Paxil*, no patients committed suicide. In pooled analyses of the pediatric placebo-controlled trials, a difference was seen between *Paxil* and placebo in suicidal thinking and suicide attempts. The incidence of adverse events possibly related to suicidal behavior while on therapy (treatment phase plus taper phase) was 2.4% (18/738) of patients treated with *Paxil* compared to 1.1% (7/647) for placebo. 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 3.4% (25/738) of patients treated with *Paxil* and 1.2% (8/647) in the placebo group. Please refer to Table 5 for incidence of events by disorder.

- In additional analyses of the depression rating scale suicide items, no statistically significant difference was seen between *Paxil* and placebo. Please refer to Table 6 for these results

how do these compare with other types

Some information contained in this response may be outside the approved Prescribing Information for *Paxil CR* or *Paxil*. This response is not intended to offer recommendations for administering *Paxil CR* or *Paxil* in a manner inconsistent with its approved labeling. In order for GlaxoSmithKline to monitor the safety of *Paxil CR* or *Paxil*, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the Prescribing Information for *Paxil CR* or *Paxil*.

BACKGROUND

In the US, major depressive disorder (MDD) has a lifetime prevalence of 16.2% and a 12-month prevalence of about 6.6% in adults (2). The average age of onset is during the late twenties, however by adolescence the prevalence of depression is approximately 5% (3, 4). After puberty, depression occurs twice as often in females than males (2, 5). Major depressive disorder is strongly associated with anxiety disorders in adults and pediatrics (6). Obsessive compulsive disorder (OCD) is rare in children, however by late adolescence the prevalence is similar to that of adults. The incidence of social anxiety disorder in pediatrics may be as high as 4% based upon DSM-IV criteria. The prevalence of depression and anxiety disorders increases around the time of puberty. Depression and anxiety disorders in children and adolescents may continue into adulthood if left untreated.

PUBLISHED LITERATURE

Placebo-Controlled Clinical Trials

Table 1: Major Depressive Disorder

Ref	Patient Population Study Design	Drug Regimen	Results	Safety Profile
7	Study 329 • N = 275 • 8 week; DB, PC, MC • Ages: 12-18 years • DSM-IV criteria for MDD Inclusion • HAM-D total score ≥ 12 • < 60 on Children's Global Assessment Scale (C-GAS) • ≥ 80 on Peabody Picture Vocabulary Test Exclusion • Current or lifetime dx of bipolar, schizoaffective, eating disorder, EtOH or substance abuse, OCD, autism-pervasive development disorder • PTSD within 12 months • Current suicidal ideation with intent or specific plan, hx of suicide attempts by overdose • Current psychotropic drug use • Adequate trial of antidepressant med within 6 months Primary Endpoints: • HAM-D ≤ 8 or ≥ 50% reduction from baseline on the HAM-D • Change from baseline in HAM-D total scores at endpoint Secondary Endpoints: • Change in depressed mood item HAM-D • Responders defined as CGI-I score of 1 or 2 • Mean CGI-I • Change in depression item of K-SADS-L • 9-item depression subscale of the K-SADS-L	• PXL 20mg/day (n=93) [max dose=40mg/day] – PXL 30-40 mg/day could be administered in divided doses at clinician's discretion • IMP 20Omg/day (n=95) [max dose = 30Omg/day] • pb (n=87)	Mean Endpoint Dose PXL 28 mg; IMP 205.8 mg Primary Endpoints (LOCF): • HAM-D ≤ 8 or ≥ 50% reduction from baseline on the HAM-D: PXL 66.7% vs. pb 55.2% (NS); IMP 58.5% (NS) • HAM-D ≤ 8: PXL 63.3% vs. pb 46.0% (p = 0.02), IMP 50.0% (NS) • Change from baseline in HAM-D total scores: PXL vs. pb (NS); IMP vs. pb (NS) Secondary Endpoints (LOCF): • Change in depressed mood item HAM-D: PXL vs. pb (p = 0.001); IMP vs. pb (NS) • CGI-I score of 1 or 2: PXL 65.6% vs. pb 48.3% (p = 0.02); IMP 52.1% (NS) • Mean CGI-I: PXL vs. pb (NS); IMP vs. pb (NS) • Change in depression item of K-SADS-L: PXL vs. pb (p = 0.05); IMP vs. pb (NS) • 9-item depression subscale of the K-SADS-L: PXL vs. pb (NS); IMP vs. pb (NS)	Premature discontinuation rates: • IMP 40% (p = 0.06 vs. pb) • PXL 28% • pb 20% Discontinuation due to AEs: • IMP 31.5% • PXL 9.7% • pb 6.9% Treatment Phase AEs (≥ 5% and twice the rate of pb): • PXL vs. pb: 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%), tooth disorder (5.4% vs. 2.3%) • IMP vs. pb: dizziness (47.4% vs. 18.4%), dry mouth (15.3% vs. 13.8%), tachycardia (18.9% vs. 1.1%), tremor (14.7% vs. 2.3%), postural hypotension (13.7% vs. 1.1%), insomnia (13.7% vs. 4.6%), somnolence (13.7% vs. 3.4%) constipation (9.5% vs. 4.6%), dyspepsia (9.5% vs. 4.6%), abnormal vision (7.4% vs. 2.3%), vasodilation (6.3% vs. 2.3%), sweating (6.3% vs. 1.1%), chest pain (5.3% vs. 2.3%) Serious AEs: detailed description below Table 1

Misrep. to reps

Ref	Patient Population Study Design	Drug Regimen	Results	Safety Profile
8, 9	Study 377 • N = 286 • 12 weeks, DB, PC, MC • Ages 12-18 years • DSM-IV criteria for MDD Inclusion • Total HAM-D ≥ 12 • ≤ 60 C-GAS • ≥ 16 on MADRS Exclusion • Pts who in the investigator's opinion had not entered puberty • Persistent conduct disorder in childhood • Autism or pervasive dev elopment disorder • Current organic psychiatric disorder, including schizophrenia and epilepsy • Serious suicidal ideation (Pts with hx of suicide attempt but who were considered a significant low risk now, could be included.) • OCD, panic, social phobia or PTSD which had preceded the dx of depression • Current psychotropic drug use • Substance dependence or hx of dependency in the previous 6 months • Long-term use of any other drug with CNS activity • Previous tx with paroxetine Primary endpoints • ≥ 50% reduction in MADRS • Change in baseline K-SADS-L Secondary endpoints: • Change in MADRS total score • Change in CGI-S • CGI global improvement score • Change in BDI • Change in MFQ	• PXL 20-40 mg/day (n=187) • ph (n=99)	Mean Endpoint Dose: 25.8 mg Primary Endpoints (LOCF): • ≥ 50% reduction in MADRS (LOCF): PXL 60.5% vs. ph 38.2% (p = 0.702) • Change in baseline K-SADS-L: PXL vs. ph (NS) Secondary endpoints (LOCF): • Change in MADRS total score: PXL vs. ph (NS) • Change in CGI-S: PXL vs. ph (NS) • CGI global improvement score: PXL vs. ph (NS) • Change in BDI: PXL vs. ph (NS) • Change in MFQ: PXL vs. ph (NS)	Treatment Phase AEs ≥ 5% and twice the rate of ph) (PXL vs. ph) • Decreased appetite (7.7% PXL vs. 1.2% ph)

PXLCTR247

Ref	Patient Population Study Design	Drug Regimen	Results	Safety Profile
10	Study 701 • N= 203 • 8 weeks, DB, PC, MC • Ages 7-17 years • DSM-IV criteria for MDD Inclusion • CDRS-R total score ≥ 45 Exclusion • Clinically predominant Axis I disorder other than MDD • Hx of psychotic episode or disorder • Hx of bipolar disorder, mental retardation or pervasive development disorder • Substance abuse or dependence within prior 3 months or test positive for illicit drugs • Pts who posed a suicidal or homicidal risk • Pts with epilepsy • Current psychotropic drug use • Those requiring concurrent psychotherapy • Hx of non-response to SSRI Primary endpoint: • Change from baseline in CDRS-R total score Secondary endpoints: • Responders defined as CGI-I score of 1 or 2 • Change in CGI-S • Change in GAF	• PXL 10-50 mg/day (n=101) • pb (n=102)	Mean Endpoint Dose, 28.3 mg Primary Endpoint (LOCF): • Change from baseline in CDRS-R: PXL -22.6 vs. pb -23.4; 0.80 points in favor of pb ($p = 0.684$) Secondary endpoints (LOCF): • CGI score of 1 or 2: PXL 48.5% vs. pb 46% (NS) • Change in CGI-S: PXL vs. pb (NS) • Change in GAF: PXL vs. pb (NS)	Treatment Phase: AEs (2.5% and twice the rate of pb) (PXL vs. pb) • Cough increased (5.9% vs. 2.9%) • Dyspepsia (5.9% vs. 2.9%) • Vomiting (5.9% vs. 2.0%) • Dizziness (5.0% vs. 1.0%)

AEs = adverse events; BDI = Beck Depression Inventory, BZD = benzodiazepines; CGI-I = Clinical Global Impression Improvement Scale; CGI-S = Clinical Global Impression Severity Scale, DB double blind; GAF = Global Assessment of Functioning Scale; HAM-D = Hamilton Depression Rating Scale; hx = history, IMP = imipramine; K-S ADS-L = Kiddie Schedule for Affective Disorders and Schizophrenia for School-age Children – Lifetime version; LOCF = last observation carried forward; MADRS = Montgomery Asberg Depression Rating Scale, MFQ = Mood and Feelings Questionnaire, CDRS-R = Children's Depression Rating Scale-Revised; MDD = Major Depressive Disorder; MC = multicenter, OC = observed cases; pb = placebo; PC = placebo controlled; PXL = *Paxil*; tx = treatment

In the study by Keller et al (7), an adverse event was defined as serious if it resulted in hospitalization, was associated with suicidal gestures, or was described by the treating physician as serious. Serious adverse events occurred in 11 patients in the *Paxil* group, 5 patients in the imipramine group, and 2 patients in the placebo group. The serious adverse events in the *Paxil* group consisted of headache during discontinuation taper (n = 1) and various psychiatric events (n = 10): worsening depression (n = 2), emotional lability (e.g., suicidal ideation/gestures) (n = 5), conduct problems or hostility (e.g., aggressiveness, behavioral disturbance in school) (n = 2), and euphoria/expansive mood (n = 1). Seven of these patients in the *Paxil* group were hospitalized due to either worsening depression (n = 2), emotional lability (n = 2), conduct problems (n = 2), or euphoria (n = 1). Of the serious adverse events only headache was considered by the treating investigator to be related to *Paxil* treatment. The 5 serious adverse events with imipramine were maculopapular rash, dyspnea/chest pain, hostility, emotional lability (e.g., suicidal ideation/gestures), and visual hallucinations/abnormal dreams. In the placebo group, emotional lability (e.g., suicidal ideation/gestures) and worsening depression were considered serious adverse events. There have been several commentaries published regarding this study (11, 12, 13, 14).

Table 2: Obsessive Compulsive Disorder

Ref	Patient Population Study Design	Drug Regimen	Results	Safety Profile
15, 16	Study 704 • N= 113 (ages 7-11 years); N= 88 (ages 12-17 years) • 10 week, DB, PC, MC Inclusion • OCD (DSM-IV); CY-BOCS scores ≥ 16 Exclusion • Any Axis I disorder other than OCD • Concurrent ADD • Current suicidal or homicidal risk • Pervasive developmental disorder or with any history of a psychotic episode, including schizophrenia and bipolar disorder Primary Endpoint: • Change from baseline in CY-BOCS Secondary Endpoints: • Responders defined as ≥ 25% reduction in CY-BOCS • Responders defined as CGI-I score of 1 or 2 • Change in CGI-S • Change in GAF	• PXL 10-55mg/day (n=98); initiated at 10 mg/day and increased by 10mg/day at weekly intervals • pb (n=115)	Mean Endpoint Dose: 24 mg Primary Endpoint (LOCF): • Change in CY-BOCS: Baseline: PXL 24.4; pb 25.1 Endpoint: PXL 15.1; pb 19.4 ($p = 0.002$) Secondary Endpoints (LOCF): • Responders based CY-BOCS: PXL 64.9%; pb 41.2% ($p = 0.002$) • Responders based on CGI: PXL 46.9%; pb 13.3% ($p = 0.001$) • Change in CGI-S (NS) • Change in GAF (NS)	Treatment Phase: Vit (≥ 5% and twice the rate of pb) (PXL vs. pb) • Hyperkinesia (12.2% vs. 5.2%) • 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%) • Vomiting (6.1% vs. 1.9%) • Agitation (5.1% vs. 1.9%) • Neurosis (5.1% vs. 1.0%)
17, 18, 19, 20	Study 453 • N=167 (ages 8-11 years) • N= 168 (ages 12-17 years) • 28-week 2 phase study: • 16 week open label • Responders continued in a 16 week DB, PC extension PXL (N = 98); pb (N = 98) Inclusion • OCD (DSM-IV); CY-BOCS scores ≥ 16 Exclusion • Any Axis I disorder other than OCD • Current, serious suicidal or homicidal risk Primary Endpoints: • Responders to open label PXL treatment defined as ≥ 25% ↓ in CY-BOCS score and CGI-I score of 1 or 2 • Relapse defined as any worsening of CGI-I score for 2 consecutive visits or worsening of 2 or more points at any single visit. Secondary Endpoints: • Change in CY-BOCS	• PXL 10-60mg/day initiated at 10 mg/day and increased by 10mg/day at weekly intervals	Primary Endpoints (LOCF): • 68.7% PXL responders from open label phase • Relapse rates: PXL 14.7% vs. 43.9% pb (p=0.176) Secondary Endpoint (LOCF): • Change in CY-BOCS baseline 26.3, open label ph ↓ by 13 DB Phase: 28.9% PXL had ↓ vs 14.4% pb ($p = 0.023$)	Treatment Phase: Vit (≥ 5% and twice the rate of pb) (PXL vs. pb) in DB phase • Hostility (6.1% vs. 0%) • Dysmenorrhea (6.1% vs. 0%)
ADHD = Attention Deficit Hyperactivity Disorder; AE = adverse events; CGI-I = Clinical Global Impression Improvement Score; CGI-S = Clinical Global Impression Severity Score; CY-BOCS = Children's Yale-Brown Obsessive Compulsive Scale; DB = double blind; dx = diagnosis; GAD = generalized anxiety disorder; LOCF = last observation carried forward; MC = multicenter; MD = major depression; MDD = Maudsley Obsessive Compulsive Inventory; OCD = Obsessive Compulsive Disorder; pb = placebo; PC = placebo controlled; PXL = Paxil				

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Table 3: Social Anxiety Disorder

Ref	Patient Population Study Design	Drug Regimen	Results	Safety Profile
21, 22	Study 676 • N = 92 (ages 8-11 years) (children) • N = 230 (ages 12-17 years) (adolescents) • 16 week, DB, PC, MC Inclusion • DSM-IV criteria for Social Anxiety Disorder • 8-17 years Exclusion • Clinically predominant Axis I disorder other than Social Anxiety Disorder • Concurrent MDD • Hx of psychotic episode, including schizophrenia & bipolar • Pervasive development disorder • Substance abuse or dependence within prior 3 months or test positive for illicit drugs • Pts with a suicidal or homicidal risk • Current psychotropic drug use or psychotherapy Primary Endpoint: • Responders, defined as CGI-I score of 1 or 2 Secondary Endpoints: •Change in CGI-S • Change in LSAS-CA total score • Change in D-GSADS-A total score • Change in SPAI or SPAI-C •Change in GAF	• PXL 10-50mg/day (n = 165, mean age 13 years), initiated at 10 mg/day and increased by 10mg/day at weekly interval • pb (n=157; mean age 13.3 years)	Mean endpoint dose: Overall: PXL 32.6 mg/day Children: PXL 26.5 mg/day Adolescents: PXL 33 mg/day Primary Endpoint (LOCF): • CGI-I responders, PXL 77.6% vs. 38.7% ($p < 0.001$). Secondary Endpoints (LOCF): • Significant improvement with PXL vs. pb on all other endpoints • Change in CGI-S PXL > pb ($p < 0.001$) • Change in LSAS-CA total score: PXL -48.01 vs. pb -24.25 ($p < 0.001$) • Change in D-GSADS-A total score PXL -42.91 vs. pb -21.08 ($p < 0.001$) • Change in SPAI or SPAI-C PXL - 17.53 vs. pb -8.11 ($p < 0.001$) • Change in GAF PXL 17.11 vs. pb 8.37 ($p < 0.001$)	Treatment Phase AEs (≥ 5% and twice the rate of pb) (PXL vs. pb). • Insomnia (14.1% vs. 5.8%) • Decreased appetite (8.6% vs. 3.2%) • Vomiting (6.7% vs. 1.9%)

AEs = adverse events; CGI-I = Clinical Global Impression Improvement Scale; CGI-S = Clinical Global Impression Severity Scale; DB = double blind; D-GSADS-A = Dalhousie Generalized Social Anxiety Disorder Scale for Adolescents; GAF = Global Assessment of Functioning Scale; hx = history; LSAS-CA = Liebowitz Social Anxiety Scale for Children and Adolescents; SPAI = Social Phobia and Anxiety Inventory; SPAI-C = Social Phobia and Anxiety Inventory for Children; LOCF = last observation carried forward; MC = multicenter; pb = placebo; PC = placebo controlled; PXL = Paxil

Analyses of Events Possibly Related to Suicidal Behavior

In the GlaxoSmithKline (GSK) pediatric trials, which included more than 1,100 patients (aged 7 to 18 years) treated with *Paxil*, no patients committed suicide (23, 24). Post-hoc statistical analyses of the placebo-controlled portions of six pooled GSK pediatric studies (detailed in Tables 1, 2 and 3) 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 departed from the conventional methods of gathering adverse event data. The method employed 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). Subjects with post-randomization suicide attempts and subjects with new or worsening suicidal ideation occurring after randomization were included in the clinical analyses. These analyses of adverse events possibly related to suicidal behavior were not prospectively designed. As relevant and potentially contributing clinical factors therefore can not be taken into account, use of different analytic methods may produce different results.

In pooled analyses of the pediatric placebo-controlled trials, a difference was seen between *Paxil* and placebo in suicidal thinking and suicide attempts (Table 5) (23, 24). There were two 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 2.4% (18/738) for *Paxil* and 1.1% (7/647) for placebo in the overall population. The analyses of 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 3.4% (25/738) for *Paxil* and 1.2% (8/647) for placebo. 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. This data is currently under review by the FDA and further analyses are being conducted. Therefore, the following information may change as more information is gathered.

Table 5: Incidence of Events Possibly Related to Suicidal Behavior in Controlled Pediatric Studies

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)		
	Paxil	Placebo	*p*-value	*Paxil*	Placebo	*p*-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

An analysis of the depression rating scale suicide items utilized in the three depression trials previously described was conducted (23). Each of these three studies used a different depression rating scale. The suicide items included: item 3 of the Hamilton Depression Rating Scale (HAM-D) in Study 329, item 10 of the Montgomery-Asberg Depression Rating Scale (MADRS) in Study 377 and item 15 of the

Children's Depression Rating Scale-Revised (CDRS-R) in Study 701. An analysis of the suicide items did not show a statistically significant change from baseline to endpoint between *Paxil* and placebo, in either the combined dataset or in each depression study alone.

A subset of patients from the three pediatric depression 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 as having a baseline score of 0 or 1 for the HAM-D and MADRS or a score of 1 or 2 for the CDRS-R which increased to ≥ 3 at any post-baseline assessment (Table 6). Results from this analysis demonstrated that there were no statistically significant differences between the *Paxil* and placebo groups in the number of patients with treatment-emergent suicidal ideation. This was the case with all three 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.

Denying suicidal with.

Table 6: Analysis of Emergent Suicidal Ideation in the Pediatric Depression Controlled Trials

Major Depressive Disorder Studies	*Paxil* % (n/N)	Placebo % (n/N)	Odds Ratio	95% CI	*p*-value
All 3 Depression Studies	9.9% (23/232)	10.2% (18/177)	0.97	0.51, 1.86	0.93
Study 329	5.8% (4/69)	1.8% (1/55)	3.32	0.36, 30.6	0.29
Study 377	4.8% (4/83)	10.6% (5/47)	0.43	0.11, 1.67	0.22
Study 701	18.8% (15/80)	16% (12/75)	1.21	0.53, 2.79	0.65
n = number of patients with "emergent suicidal ideation" as defined above N = total number of patients without baseline suicidal ideation in treatment arm					

With respect to adults, the FDA has acknowledged that there is no evidence that *Paxil* is associated with an increased risk of suicidal thinking or behavior in adults.

Long-Term Safety

Gallagher et al (25, 26) reported on the long-term safety and tolerability of *Paxil* in children and adolescents (7-17 years of age) with OCD or MDD. Patients with OCD or MDD that had completed either an acute, placebo-controlled *Paxil* trial or an open-label, repeat-dose *Paxil* pharmacokinetic trial were eligible to participate in a 6-month, open-label, extension trial (n = 263, 147 with MDD and 116 with OCD). Safety was assessed by the incidence of adverse events reported. The overall mean daily dose of *Paxil* was 22.9 mg/day while the mean daily dose in children was 20.9 mg/day and in adolescents 25.0 mg/day. Common adverse events (incidence ≥ 10%) experienced during extension phase treatment with *Paxil* were headache (25.1%), respiratory disorder (18.3%), trauma (15.7%), infection (12.5%), pharyngitis (10.6%) and abdominal pain (10.3%).

Pharmacokinetics

A multicenter, open-label study was conducted to assess the pharmacokinetics of repeat dose *Paxil* in children and adolescents with OCD and/or MDD (27). Evaluated endpoints included steady state pharmacokinetic profile of repeat doses of *Paxil*, along with safety and tolerability. There were 27

children (7 to 11 years) and 35 adolescents (12 to 17) who entered the study and received medication. *Paxil* was dosed initially at 10 mg/day for 14 days, then 20 mg/day on days 15-28 and then titrated to 30 mg/day for days 29-42. *Paxil* was then tapered down to 10 mg/day before stopping therapy (taper period optional). Pharmacokinetic sampling was obtained over approximately 24 hours following the final dose at each dosing level during the dose escalation stage. In both children and adolescents steady-state Cmax and area under the curve (AUC) increased disproportionately with dose. Cmax and AUC were higher and clearance was lower in children compared to adolescents. Tmax values suggested no difference in absorption rate between children and adolescents. *Paxil* was generally found to be well-tolerated by pediatric patients (8 to 17 years). The most common adverse events were headache (18.5%), abdominal pain (7.4%) and somnolence (6.0%) in the overall population.

Table 7: Summary of Paroxetine Steady-State Pharmacokinetic Parameters

Parameter (units)		Children			Adolescents		
		10 mg (n=23)	20 mg (n=23)	30 mg (n=21)	10 mg (n=35)	20 mg (n=29)	30 mg (n=27)
Cmax (ng/mL)	Mean (SD)	19.5 (18.2)	58.6 (34.5)	129.0 (106.9)	12.0 (13.0)	42.7 (30.0)	94.0 (51.4)
Tmax (hours)	Median	4.9	5.0	3.E	5.0	5.0	3.3
AUC (0-24) (ng/mL)	Mean (SD)	285 (291)	899 (552)	2081 (1737)	189 (227)	735 (581)	1631 (1040)

Findling et al (28) conducted an 8-week, open-label study to assess the pharmacokinetics and safety of *Paxil* in 30 adolescents (5 to 17 years) with MDD (DSM-IV criteria). In addition to DSM-IV criteria, younger patients (≤ 12 years) needed a score of at least 40 on the CDRS and older subjects were required to have a HAM-D ≥ 17. Patients were initiated on *Paxil* 10 mg/day. After four weeks, the dose could be increased to 20 mg/day based on response. Following a single dose of *Paxil* 10 mg, the mean Cmax, Tmax, half-life and AUC were 5.5 ng/mL (SD 4.0), 5.7 hr (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 *Paxil* 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 *Paxil* 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. The focus of this study was on the pharmacokinetic and safety profile of *Paxil* in children and adolescents. Therefore, efficacy results in terms of changes in the HAM-D and CDRS were not assessed. Overall, adverse events were mild and transient; gastrointestinal events (e.g., nausea, abdominal cramps) were reported most commonly. There were no clinically significant changes in weight, blood pressure, pulse, electrocardiogram, serum chemistry and hematological studies noted.

Non-Placebo-Controlled Published Literature

There are several additional non-placebo-controlled studies evaluating the efficacy and/or safety of *Paxil* in the treatment of children and adolescents with MDD (29, 30, 31, 32). In these studies, *Paxil* was generally well tolerated and patients showed improvement in their depressive symptoms. Two 12-week, open-label studies assessed the efficacy of *Paxil* in pediatric patients with OCD (33, 34). Patients had significant improvement at endpoint in OCD symptom severity. The adverse events were similar to those reported in the larger, placebo-controlled studies previously discussed. In addition, two small studies in panic disorder were identified; study details are presented in Table 8.

Table 8: Panic Disorder

Ref	Patient Population Study Design	Drug Regimen	Results	Safety Profile
35	• N = 18 • Ages 7-16 years • Retrospective review • Panic disorder (DSM-IV criteria) • 55.6% with comorbid GAD • Clinical status assessed at every visit with 5-point CGI-S	• PXL: mean initial dose: 8.9 mg day, gradually increased to 40 mg day based on response and AEs • mean final dose: 23.9 mg day • 12 month treatment duration (mean = 11.7 months)	• Based on CGI: 85.7% of patients responded (p = 0.001) at study endpoint	Common AEs (criteria undefined): • nausea (n=7, 38.8%) • tension-agitation (n=7, 38.8%) • sedation (n=6, 33.3%) • insomnia (n=4, 22.2%) • palpitations (n=4, 22.2%) • headache (n=4, 22.2%)
36	• N= 32 (ages 7-17 years) • Naturalistic, open-label with 2 phases (acute treatment for 6-8 weeks; follow-up for 6 months) • Panic disorder (DSM-IV criteria); 8 patients with comorbid conditions (GAD, separation anxiety or social phobia) • Assessments with variety of anxiety and panic scales, CGI and CGAS.	• Number of different SSRIs: For PXL: Acute phase: n=2 PXL 20 or 60 mg day Follow-up: (n=3) PXL 10-30 mg day Concomitant BZD (n=1 treated with PXL)	• At study endpoint vs. baseline – significant improvement noted: Mean CGI-S (2.2 vs 4.4, p = 0.02) CGAS (74.3 vs. 48.5, p = 0.001) Mean time to CGI-I score of 1 or 2 was 10.5 weeks	No significant differences noted in AEs from baseline to study endpoint

AEs = adverse events; BZD = benzodiazepines; CGI-I = Clinical Global Impression Improvement Scale; CGI-S = Clinical Global Impression Severity Scale; CGAS = Children's Global Assessment Scale; GAD = Generalized Anxiety Scale; PXL = *Paxil*

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