

CLINICAL REVIEW

NDA: 20-031
SUPPLEMENT: S-037
SPONSOR: GlaxoSmithKline
DRUG: Paroxetine HCl (Paxil)
MATERIAL SUBMITTED: Pediatric Exclusivity Supplement
DATE SUBMITTED: 4-11-02
PDUFA DUE DATE: 10-11-02
REVIEW COMPLETION DATE: 10-7-02
REVIEWER: Andrew D. Mosholder, M.D., M.P.H.

Executive Summary

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- I. Recommendations
 - A. Recommendation on Approvability: In my opinion, the supplement is approvable.
 - B. Recommendation on Phase 4 Studies and/or Risk Management Steps: In my opinion, no particular Phase IV commitments are necessary.
- II. Summary of Clinical Findings
 - A. Brief Overview of Clinical Program

This supplement included data from three acute treatment randomized controlled trials in pediatric major depressive disorder (MDD), one acute treatment trial in pediatric obsessive compulsive disorder (OCD), one relapse prevention trial in OCD, and open label treatment. Preliminary safety findings from a recent study in pediatric social phobia were also included. The table below lists the trials.

Study	Description
Social Phobia	
676	Randomized, double blind, placebo controlled, parallel group, 16-week trial; paroxetine 10-50 mg/day versus placebo; n=328 children and adolescents with social phobia. Study completed but only data on serious adverse events available for this submission.
MDD	
329	Randomized, double blind, placebo controlled, parallel group, 8 week trial; paroxetine 20-40 mg/day versus placebo; n=275 adolescents aged 12-18 years with MDD. Continuation phase allowed for up to 6 months of additional double blind medication.
377	Randomized, double blind, placebo controlled, parallel group, 12 week international trial; paroxetine 20-40 mg/day versus placebo; n= 275 adolescents aged 13-18 years with MDD
701	Randomized, double blind, placebo controlled, parallel group, 8 week trial; paroxetine 10-50 mg/day versus placebo; n=203 children and adolescents with MDI

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Obsessive Compulsive Disorder	
453	Randomized, double blind, placebo controlled, 16 week relapse prevention trial; 16 week open label treatment with paroxetine followed by randomization of responders to placebo or paroxetine 10-60 mg/day; n= 335 children and adolescents with OCD (in double blind phase)
704	Randomized, double blind, placebo controlled, parallel group, 10 week trial; paroxetine 10-50 mg/day versus placebo; n=203 children and adolescents with OCD
Open label safety	
716	Open label, 6 month extension for subjects in studies 701, 704 or 715; paroxetine 10-15 mg/day; n= 261 children and adolescents with MDD or OCD. Study ongoing as of 10-1-01 cutoff date.
Pharmacokinetic	
715	Open label, multiple rising dose pharmacokinetic study; paroxetine 10-30 mg for up to 10 weeks; n=62 children and adolescents with either MDD or OCD

The integrated safety database for this supplement included data on 932 pediatric patients treated with paroxetine, for a total exposure of 283 patient-years.

B. Efficacy

The three randomized, controlled trials in MDD, listed above, all failed to show a separation of paroxetine treatment from placebo on their primary efficacy measures.

Study 377: There were a total of 33 sites in 10 different countries (Belgium, Italy, Spain, U.K., Holland, Canada, South Africa, United Arab Emirates, Argentina, and Mexico). The objective of this study was to evaluate the safety and efficacy of paroxetine in the treatment of adolescent unipolar major depression. The initial phase of the study was a 2-week placebo washout. Following this, subjects were to be randomized to 12 weeks of treatment with either paroxetine or placebo; dosing of paroxetine was flexible (20, 30 or 40 mg daily). Subjects were then tapered off study medication over a 2 week period. The sample was to be 264 outpatients with unipolar major depression, aged 13-18 years. The two primary outcome measures were (1) the proportion of subjects with at least a 50% reduction from baseline in their Montgomery Asberg Depression Rating Scale (MADRS) score, and (2) change from baseline in the K-SADS-L depression subscale. A total of 182 subjects received paroxetine and 93 received placebo. The sample was predominantly female (gender ratio approximately 2:1) and Caucasian, with a mean age of approximately 15 years. There were no obvious imbalances between treatment groups with respect to demographic characteristics. The results for the primary outcome measures failed to distinguish between paroxetine and placebo. The proportion of patients meeting the response criterion was 60% for paroxetine and 58% for placebo (p-value = 0.62). The mean change from baseline in K-SADS-L depression subscale was -9.3 for paroxetine and -8.9 for placebo (p-value = 0.70). **Conclusions:** This trial did not provide any evidence that paroxetine is active in the treatment of adolescent MDD.

Study 701: There were 40 U.S. sites and one Canadian site for this trial. The objective of this trial was to compare the safety and efficacy of paroxetine and placebo in the treatment of children and adolescents with MDD. This was a randomized, double blind, placebo controlled, parallel group, flexible dose study. Subjects were to have a screening evaluation followed by a baseline evaluation approximately one week later, and if eligible were then randomized to receive either paroxetine 10-50 mg/day or placebo, for a duration of 8 weeks. Randomization was to be stratified by age group (7-11 years, and 12-17 years). The initial dose was to be 10 mg

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daily for all subjects, with dose increases permitted weekly in increments of 10 mg, up to the maximum of 50 mg. At the end of the study the dosage was down-titrated by 10 mg/day every 7 days, with discontinuation after subjects received 10 mg for one week. The protocol specified the following as the primary outcome measure: "Change from baseline in Children's Depression Rating Scale - Revised (CDRS-R) total score at the Week 8 LOCF endpoint." The intended sample size was 192. Subjects were to have MDD, with a CDRS-R score of at least 45 at both baseline and screening. Three hundred five subjects were screened, and 206 were randomized (104 to paroxetine and 102 to placebo). There were slightly more premature discontinuations in the paroxetine group (31) than in the placebo group (23). On the mean change from baseline at endpoint in CDRS-R total score, which was the primary outcome measure, the result for the placebo group was numerically superior to that for the paroxetine group (-23.4 versus -22.6 for placebo and paroxetine, respectively). With respect to secondary outcome measures, there were no results showing statistical superiority of paroxetine over placebo. Conclusions: This trial did not provide any evidence that paroxetine is effective in the treatment of pediatric MDD.

Study 329

There were 13 U.S. sites for this trial. The purpose of this trial, as stated in the protocol, was to "compare the efficacy and safety of imipramine and paroxetine to placebo in the treatment of adolescents with unipolar major depression." This was a multicenter, randomized, double-blind, placebo controlled, three-arm, parallel group study. The duration of acute treatment was to be 8 weeks, with the option of a 6-month extension of double blind treatment for subjects who had responded. After a 7-10 day screening period eligible subjects were to be randomized to imipramine, paroxetine, or placebo. The randomization ratio was 1:1:1, with randomization in blocks of 6 subjects. The titration scheduled specified an initial daily dose of imipramine of 50 mg, with titration to 200 mg by the beginning of the fourth week. The dosage of paroxetine was 20 mg which was to be initiated without titration. In the event of inadequate response by the end of 4 weeks, the medication could be titrated up to 300 mg of imipramine or 40 mg of paroxetine. Medication was administered in divided doses on a BID schedule. Concomitant psychotropic medications were prohibited. There were two primary outcome measures specified: the change in HAMD 17 item total score at endpoint, and the proportion of responders at endpoint. A subject was to be considered a responder at week 8 if he or she had a HAMD-17 score ≤ 8 , or a decrease from baseline in the HAMD-17 of at least 50%. The subjects were to be 300 adolescents, aged 12-18 years, with MDD according to DSM-III-R criteria, and a minimum HAMD-17 score of 12. The current episode of major depression was to be at least 8 weeks in duration. Ninety patients were randomized to paroxetine, 94 to imipramine, and 87 to placebo. Adverse events were the most frequent reason for discontinuation from the imipramine arm; otherwise there were not major differences in the disposition of subjects between treatment groups. Over 70% of paroxetine and placebo patients completed the trial. The result on the HAMD for the paroxetine arm was numerically superior to the other treatment groups; but the difference was not statistically significant. For the second primary outcome measure, the proportion of patients who met the aforementioned criteria for response (HAMD-17 score ≤ 8 , or a decrease from baseline in the HAMD-17 $\geq 50\%$), the proportion of responders at endpoint was greater for paroxetine than placebo, but this difference was not statistically significant. The difference in the proportion of responders was, however, marginally statistically significant using an observed cases analysis. On the secondary outcome measure of remission, the percentage of patients with a HAMD score ≤ 8 at endpoint, the result was 63.3% for paroxetine, 50.0% for imipramine, and

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46.0% for placebo. On this outcome the difference from placebo was statistically significant for paroxetine (p-value = 0.019) but not for imipramine. On the CGI-Improvement scale, the results showed superiority of paroxetine over placebo by a statistically significant margin for the observed cases analysis, but not for the LOCF analysis. Conclusions: Although there was some evidence of activity of paroxetine on the secondary outcome measures, the paroxetine treatment group did not separate statistically from placebo on the a priori primary efficacy measures in this trial. There was no evidence that imipramine was more effective than placebo in this trial. On balance, this trial should be considered as a failed trial, in that neither active treatment group showed superiority over placebo by a statistically significant margin.

FDA
dispute
329 rejected
final.

OCD Study 704:

Please refer to the study report for a complete list of investigators. The purpose of this study was to determine the safety and efficacy of paroxetine for the treatment of pediatric OCD. This was a randomized, double blind, multicenter, parallel group, flexible dose study. Subjects were to have a screening assessment, followed in approximately one week by a baseline assessment. If subjects met the entry criteria at the baseline evaluation, they were randomized to either paroxetine or placebo. Randomization was to be stratified by 2 age subgroups (7-11 years of age versus 12-17 years of age). The initial dosage of paroxetine was to be 10 mg daily, which could be increased by 10 mg/day at weekly intervals as needed, up to a maximum of 50 mg/day. Placebo patients could receive one to five tablets of matching placebo per day. The duration of the acute treatment phase was to be 10 weeks. There was to be no concomitant psychotropic medication, or concomitant psychotherapy. When discontinuing treatment, subjects were to be down-titrated by increments of 10 mg per week until they had remained on 10 mg/day for 7 days; at that point the medication was stopped. Optional open label treatment, up to 6 months in duration, was to be made available to subjects following the trial (under Protocol 716). Subjects were to be assessed every 1-2 weeks during the acute treatment phase of the trial; efficacy assessments included CY-BOCS and CGI (Severity and Improvement). Subjects were to be between 7 and 17 years old, with OCD for at least 2 month's duration. The goal was to randomize roughly equal numbers of children (aged 7-11 years) and adolescents (aged 12-17 years), with a total of 204 subjects. OCD was to be the primary psychiatric diagnosis, and the CY-BOCS score was to be at least 16 at both the screening and baseline visits. The change from baseline in the CY-BOCS (LOCF at week 10) was designated the primary outcome variable. The study was conducted from January 2000 through July 2001. Of the 265 subjects who were screened, a substantial majority (207) were randomized, 98 to paroxetine and 105 to placebo. Overall, the sample was predominantly male (117 males and 86 females). The mean age of the children was approximately 9 years for both paroxetine and placebo groups, and the mean age of the adolescents was approximately 14 years. The sample was predominantly Caucasian (88%); 6% of subjects were African-American, and the remainder "other." There were no Asian subjects in the trial. The median duration of OCD was 3 years. Psychiatric comorbidity of some type was present in 31% of paroxetine patients and 40% of placebo subjects. The mean daily dose of paroxetine at endpoint was 30.1 mg/day for the entire sample, and was slightly higher for adolescents (36.5 mg/day) than for children (25.4 mg/day). On the primary outcome variable, the week 10 LOCF mean change from baseline in CYBOCS for the intent-to-treat sample, the results were as follows.

	Paroxetine	Placebo
N (ITT sample)	91	98

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Baseline LS mean	24.2	25.1
Mean change, LOCF, wk 10	-9.3	-5.5
p-value (ANCOVA)	<0.001*	

* adjusted for baseline score, age group, gender, and psychiatric comorbidity

Conclusions: This trial provides evidence that paroxetine is active in the treatment of pediatric OCD.

OCD Study 453: There were a total of 26 investigators for this trial. All sites were in the U.S. The purpose was to assess the effect of paroxetine treatment on relapse in pediatric OCD patients. This was a multicenter, randomized, double blind, placebo controlled trial. The first phase of the study was to be an open label, 16 week period of treatment with paroxetine. Subjects were administered a starting dose of 10 mg/day, and the dose could be increased to a maximum of 60 mg/day. At the end of the 16 weeks of treatment, subjects were to be randomized to either placebo or paroxetine if they met the following criteria: at least a 25% improvement from baseline on the CYBOCS total score, and a CGI-improvement score of 1 or 2. The dosage during the double blind portion of the trial was not to be adjusted. Subjects who were randomized to placebo were to be down-titrated blindly in increments of 10 mg per week. At the end of double blind treatment, subjects were down-titrated in a similar fashion. The duration of double blind treatment was to be 16 weeks. During the double blind portion of the trial, a subject was to be withdrawn from the trial and referred for treatment if they met any of these criteria: worsening of CGI-improvement score by 1 point for 2 consecutive visits, worsening of CGI-improvement score by >2 points at any visit, or CGI-improvement score >5. The subjects were to be aged 8-17 years, with OCD by DSM-IV criteria as their primary diagnosis, confirmed by the K-SADS-L. The goal was to enroll 375 subjects in open label treatment, with the expectation that 180 of these subjects could subsequently be randomized. Subjects were to have a score of at least 16 on the CYBOCS at both screening and baseline. The primary outcome measure was the proportion of patients who relapsed (according to the criteria above) during double blind treatment. Time to relapse was specified as a secondary analysis. A total of 339 subjects entered the open label treatment phase, and 194 of these subjects were subsequently randomized, 95 to paroxetine and 98 to placebo. The median age was 10 for the paroxetine subjects and 9 for placebo subjects. The sample was over 90% Caucasian. There was a slight gender imbalance between treatment groups; 51% of the paroxetine subjects were female, while only 41% of the placebo patients were female. The intent-to-treat sample included 193 subjects. The percentage of patients who relapsed was 35% for paroxetine and 45% for placebo; this difference was not statistically significant, however (p-value = 0.14). The results varied by age subgroup: subjects under 12 years of age showed a lower percentage of relapsers for paroxetine compared to placebo, while the percentage of relapsers was essentially equal between treatment groups for the adolescents. For time to relapse, the hazard ratio of 1.5 favored paroxetine over placebo, but this was not statistically significant (p-value = 0.10). Conclusions: This trial failed to show that paroxetine is effective in the prevention of OCD relapse in pediatric patients.

C. Safety

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The most prominent adverse reactions not seen in corresponding adult trials appear to involve behavioral effects; these events were coded with terms such as hostility and emotional lability. As previously noted, the sponsor's method of coding these events was potentially confusing, and thus additional information will be helpful for the purpose of definitively assessing the potential behavioral toxicity of paroxetine treatment in pediatric patients.

There was one postmarketing spontaneous report that described a fatal allergic reaction in an 11 year old boy following a single dose of paroxetine.

Further assessment of the safety profile will have to await the sponsor's reply to requests for additional information, such as the request regarding ECG data.

D. Dosing

The sponsor's proposed labeling recommends an initial dose of 10 mg daily with titration up to 50 mg/day as needed and tolerated. It also advises that physicians should be mindful of children's lower body weights when titrating the dosage, and that the daily dose should be advanced at a rate of 10 mg/week. This was the regimen employed in the pivotal OCD trial. However, based upon the similarities in pharmacokinetics between adolescents and adults, OCPB has recommended that the 10 mg starting dose be for children only; please refer to Dr. Jackson's review for details.

E. Special Populations: This supplement is limited to pediatric data.

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