CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-936/SE5-064

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 12, 2002

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for
the Prozac (fluoxetine) Pediatric Use Supplement

TO: File NDA 18-936/S-064
[**Note:** This overview should be filed with the 10-4-01
original submission.]

An initial supplement [redacted] for major depressive disorder (MDD) and obsessive compulsive disorder (OCD) in the pediatric population was submitted 12-12-96, [redacted]
That supplement included only the Emslie paper, in support of the MDD claim, and only a paper by Riddle, et al in support of the OCD claim. The Riddle study was admittedly negative on the primary outcome. We informed the sponsor that we would need 2 positive MDD studies, and 1 positive OCD study, with complete access to the data for all three. S-064 was the resubmission of this supplement (9-14-00), and we issued an approvable letter for S-064 on 7-12-01. In that letter, we identified several issues that needed to be addressed before we could take final action on S-064. Lilly responded in a 10-4-01 amendment, which has been reviewed by Andrew Mosholder, M.D.

Finding of Reduced Growth Velocity for Height and Weight:

-We asked Lilly to adopt labeling language describing a finding of an apparent fluoxetine-induced reduction in growth velocity for height and weight, in association with reduced levels of alkaline phosphatase, in a 19-week study (HCJE).

-We asked that they reanalyze these data using age and gender adjusted height and weight percentiles, and determine if the alkaline phosphatase changes were related to decreased bone growth.

-Finally, we asked that they commit to conducting a phase 4, long-term safety study

-Lilly Response:

-Lilly used Z-scores calculated for age and gender for a reanalysis of these data, which again yielded a statistically significant reduction in growth velocity (both height and weight) for fluoxetine vs placebo in

study HCJE. However, they did not find a correlation between change in height and change in alkaline phosphatase.
-Regarding labeling changes pertinent to these findings, Lilly has generally accepted our proposed language, with a few exceptions. They have removed the statement suggesting that the reduced alkaline phosphatase levels may reflect the reduced growth velocity, since there was no correlation. They also removed the statement suggesting that longer term fluoxetine treatment may be associated with decreased growth, since there are no systematic data beyond 19 weeks.
-However, they have declined to commit to conducting a longer-term trial to address this question. -
Comment:
-I don't object to their changes to labeling regarding reduction in growth velocity, however, I think we should continue to ask for a longer-term trial to address this question.

Discrepancy in QTc Findings:
-In an initial analysis of QTc (cube root corrected) data for the baseline to 19 week comparison in HCJE, there was a statistically significant greater increase of 7.4 msec for fluoxetine vs 0.2 msec for placebo. Subsequent re-analyses by 2 different consulting groups contracted by Lilly yielded no statistically significant differences. QTc data from the PK study (HCIU), as analyzed by ——— actually showed a decrease for fluoxetine vs placebo.
-In the 7-12-01 approvable letter, we requested that Lilly provide an explanation for these discrepant findings, and a rationale for why we should accept the later results.
-In their initial 10-4-01 response, Lilly argued that the initial findings ——— suggesting a roughly 7 msec effect for Prozac resulted from methods perhaps not appropriate for ECGs for children. These data were analyzed by adult cardiologists, using hand-held calipers. The results from ——— were also derived from measurements obtained by hand-held calipers, but apparently by child cardiologists, and the ——— findings were derived from measurements obtained using an electronic digitizing method, and using an approach to adjust for the degree of sinus arrhythmia present.
-Dr. Mosholder, in his review, did not find this argument persuasive. He noted, in particular, that one finding that distinguishes the later two analyses from the —— analysis was higher baseline QTc's.
-In trying to better understand this discrepancy, we asked for additional information from Lilly:

-We asked for the data broken out by dose groups, however, there were too few patients at doses higher than 20 mg to really make any sense out of the dose response data.

-We also asked if raters were blinded to both treatment assignment and baseline vs endpoint status; it turned out that raters were not blinded to baseline vs endpoint status, leaving open the possibility that this could have been a source of bias.

-Finally, we asked if there was evidence of a differential effect of fluoxetine and placebo on heart rate variability to explain how this factor might have influenced the differences between analyses. Lilly was unable to provide any information on group differences.

-This issue was raised by Judy Racoosin, M.D. with the QT Working Group at FDA, and their feeling was that one cannot without qualification assume that the electronic digitizing method is superior to hand-held calipers, and they also did not find the other Lilly arguments persuasive. The Working Group had several suggestions for additional data to obtain from Lilly, including:

-Inquire as to how ECG complexes were chosen to be measured by the different groups.
-Ask for a dataset with raw data lined up for each analyzer from each group.
-A list from [redacted] of the patients with sinus arrhythmias requiring the use of 5 rather than 3 complexes.
-Raw ECG data for the subgroup of patients whose readings appeared to cause the differences between the 3 groups analyzing these data.

-Comment: After internal discussion, we agreed that it will be necessary to obtain the additional data described above before we can resolve this issue, even if this means delaying a final action on this supplement.

Safety Update (Postmarketing and Literature Update):

-We asked Lilly to provide an updated literature search focusing on the safety of fluoxetine in pediatric patients, and for an update on postmarketing reports for fluoxetine in pediatric patients.

-Lilly Response:

-Lilly provided an updated literature search. Dr. Mosholder reviewed this response, and concluded that no new safety information regarding this population was revealed.

-Lilly provided an update on postmarketing reports for fluoxetine in pediatric patients. Dr. Mosholder reviewed this response, and concluded that no new safety information suggesting a unique risk in this population was revealed.

-Comment:

-I agree that no important new safety information was revealed by this safety update.

Phase 4 Commitment for PK/PD Study for QTc:

[redacted]

Satisfactory Completion of Inspection of Emslie Study:

-We alerted Lilly to the fact that we intended to inspect the Emslie site and that the satisfactory inspection of this site would be a condition of final approval.

-Comment: This inspection was completed and found to be acceptable.

Juvenile Animal Studies:

-On 1-10-01, we issued a letter to the sponsors of all the more recently approved antidepressants, including Lilly for Prozac, requesting that they conduct juvenile animal studies as part of their overall pediatric development plan. In an initial response (7-5-01), Lilly argued against the need for such a study. However, they have subsequently reconsidered, and submitted outlines on 3-8-02 for a pilot study and a "combined repeat dose general toxicity, neurobehavior and fertility study in young rats," along with a commitment to complete this program within 2 years. Our pharm/tox group has found these draft protocols acceptable, and Lilly will next submit these protocols for formal comment.

Conclusions/Recommendations:

-All of the remaining issues have been addressed, except for the discprepancy in QTc data. However, this is an issue that needs to be resolved before we can reach final agreement on labeling. Therefore, there is internal agreement that the appropriate action at this point is a second approvable letter, in which we can request the additional QTc data we need in order to resolve this discrepancy. Thus, I recommend that we proceed with issuing the approvable letter, along with our current version of labeling.

cc:
Orig NDA 18-936/S-064
HFD-120
HFD-120/TLaughren/RKatz/AMosholder/PDavid

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/s/

Thomas Laughren
3/12/02 08:30:40 AM
MEDICAL OFFICER

MEMORANDUM

DATE: January 2, 2003

FROM: Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 18-936/SE5-064

SUBJECT: Action Memo for NDA 18-936/SE5-064, for the use of Prozac (fluoxetine hydrochloride) pulvules in the treatment of pediatric patients with Major Depressive Disorder (MDD) or Obsessive-Compulsive Disorder (OCD)

NDA 18-936/SE5-064, for the use of Prozac (fluoxetine hydrochloride) pulvules in the treatment of pediatric patients with Major Depressive Disorder (MDD) or Obsessive-Compulsive Disorder (OCD), was submitted by Eli Lilly and Company on September 14, 2000. The application contained data from 2 controlled trials in pediatric patients with MDD, and one trial in pediatric patients with OCD. An Approvable letter was issued on 7/12/01, and a second Approvable letter was issued on 3/19/02.

In the second letter, we asked the sponsor to further investigate a finding of prolonged QTc interval in the precordial leads in patients with a pattern of juvenile T waves. This prolongation was seen by one of three investigators who examined the EKG data [redacted] the only investigator who examined these leads (the other 2 reviewers examined Lead II, the lead which is routinely examined for QTc prolongation). The identification of this sub-group (patients with Juvenile T waves) was made retrospectively.

In addition, the second Approvable letter noted the sponsor's commitment to perform juvenile animal studies in Phase 4, and also included a request for the sponsor to commit to performing a Phase 4 study to further characterize effects on growth in a study submitted with the application (in a 19 week study, fluoxetine patients gained about 1 cm and 1 kg less than placebo patients).

The sponsor responded to this second Approvable letter in a submission dated 7/2/02 (and subsequent submissions). These submissions have been reviewed by Dr. Gerard Boehm, safety team reviewer (reviews dated 9/7/02 and 9/19/02), Dr. Mehul Desai, cardiology consultant (review dated 8/30/02), and Dr. Judy Racoosin, safety team leader (memo dated 9/24/02).

Because the review of the sponsor's submissions did not adequately address our concerns related to the finding of a prolonged QTc interval in the subset of patients with a juvenile T wave pattern, we spoke with three cardiology experts [redacted] about this finding.

None of these experts could explain the discrepancy between the lack of such a finding in the more traditional leads and the presumed finding in the chest leads, nor were they aware of the clinical meaning of such a finding, but none were willing to dismiss the finding as meaningless. All three did suggest that a reasonable next step in the characterization would be for a blinded independent reviewer to examine the QTc interval in both Leads II and V3 (none of the previous EKG reviewers had looked at both leads).

On the basis of this suggestion, we asked the sponsor to have an independent reviewer perform this analysis.

The sponsor chose [redacted] to perform this blinded analysis. The result of this analysis was submitted by the sponsor on 12/11/02. Dr. Boehm has reviewed these re-analyses (review dated 12/30/02). Dr. Thomas Laughren, Psychiatric Drugs Team Leader, has also issued a memo (12/19/02).

Briefly, Dr. [redacted] analysis revealed no difference in the QTc interval between fluoxetine and placebo-treated patients (with or without juvenile T waves) in Lead II, but there was a nearly significant difference in V3 in the subset of patients with Juvenile T waves:

Drug	**Change from baseline in QTc**	**P-value**
Rochester		
Fluoxetine	4.14	
Placebo	-6.16	0.053
[redacted]		
Fluoxetine	8.56	
Placebo	-5.37	0.002

Although the estimate of the QTc prolongation decreased somewhat, the difference still is about 10 msec.

It is difficult to understand the meaning of this finding. It remains unclear why there should be a discrepancy between the estimate of the QTc interval in lead V3 as compared to Lead II (the traditional lead in which QTc interval duration is assessed), and, importantly, what an isolated prolongation in lead V3 means clinically. Further, it is difficult to understand how to quantify this "finding", given that the bulk of the 10 msec difference between drug and placebo is accounted for by a decrease of about 6 msec in the placebo group (which would be expected to be 0). Finally, we cannot have great confidence that the "finding" is, in reality, a true finding, given the retrospective identification of this particular

subset of patients. Given the uncertainties about whether this is a bona fide finding and, if it is, what it means clinically, we have decided to not describe this in labeling.

However, a number of these uncertainties could be the subject of further investigation.

Specifically, in a telephone conversation on 1/2/03, we have discussed with the sponsor the possible meaning of this finding, and what might be done to further evaluate the possible signal. In their view (and in the view of Dr. —, V3 is an unreliable lead in which to measure the QT interval, largely because of the difficulties in accurately locating the end of the T wave, perhaps especially in patients with a juvenile T wave pattern, and that "routinely" the interval as measured in V3 is at variance with the interval as measured in other leads. Further, the sponsor argues that Lead II is the appropriate lead in which to measure QT interval, and Dr. — notes that, in his experience with patients with congenital prolonged QT syndrome, the prolonged QT interval is most reliably assessed in Leads II, avF, and V5.

As noted above, Dr. — concludes that measurement of the QT interval in lead V3 is often at variance with the interval as measured in other leads, but this observation has not been made in this dataset. That is, only leads II and V3 have been systematically examined. He and the sponsor agreed that measurement of the QT interval in other leads (Dr. — stated that there are about 8 leads in which the QT interval could be reliably measured, especially avF and V5) could provide reassurance about the lack of reliability of V3 if these other leads gave results similar to those seen in Lead II.

A prospective study in patients with juvenile T waves would be an ideal way to further evaluate whether or not this is a true signal. However, such a study would be difficult to do for several reasons, especially because the juvenile T wave pattern is presumably intermittent in those patients who have this pattern, so that reliably identifying these patients and assessing any drug effects would be difficult. For this reason, I believe that a reasonable next step in assessing this signal would be to examine other leads in the study performed to better place the finding seen in V3 in context.

For this reason, then, I will issue the attached Approval letter, with appended labeling. In particular, the letter will describe the following Phase 4 commitments:

1) the performance of juvenile animal studies,
2) the performance of a study to examine the long-term effects on growth, and
3) the examination of the QT interval in multiple other leads; if the results are not as expected (see above), additional work may need to be done.

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/s/

Russell Katz
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MEDICAL OFFICER

MEMORANDUM

DATE: July 11, 2001

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 18-936/SE5-064

SUBJECT: Action Memo for NDA 18-936/SE5-064, for the use of Prozac (fluoxetine HCl) in pediatric patients with Major Depressive Disorder (MDD) or Obsessive Compulsive Disorder (OCD)

Supplement SE5-064 to NDA 19-936, for the use of fluoxetine in patients with MDD or OCD was submitted by Eli Lilly and Company on 9/14/00. The application contains the results of 2 controlled trials in pediatric patients in patients with MDD, and 1 controlled trial in pediatric patients with OCD. In addition, the sponsor presented safety data in this population, as well as limited pharmacokinetic data. The application has been reviewed by Dr. Andrew Mosholder, medical reviewer (review dated 6/25/01), Dr. Yuan-Li Shen, statistical reviewer (review dated 7/5/01), Drs. Vanitha Sekar and Elena Mishina, Office of Clinical Pharmacology and Biopharmaceutics (reviews dated 11/6/01 and undated, respectively), and Dr. Thomas Laughren, Psychiatric Drugs Team Leader (memo dated 7/3/01). The review team recommends that the application be considered approvable. In this memo, I will briefly describe the results of the trials, and present the rationale for the Division's action.

Major Depressive Disorder (MDD)

As noted, the sponsor presented the results of 2 short-term (Study HCJE, 9 weeks; Study X065, 8 weeks) randomized, placebo controlled trials in pediatric patients (ages 8-17) with MDD. Patients were treated with fluoxetine 20 mg or placebo. Study HCJE was a multi-center study sponsored by Eli Lilly; Study X065 was performed by Dr. Graham Emslie at the University of Texas Southwestern Medical Center. Eli Lilly was not involved with the conduct of this study, but obtained the primary data and performed their own analyses.

As all reviewers have noted, Eli Lilly presented as the primary outcome of both studies the proportion of patients achieving at least a 30% reduction from baseline in CDRS-R score at endpoint (even though this was not the protocol specified endpoint for Study X065). Also, as all reviewers have noted, the Division had previously informed the sponsor that we did not agree that this was an appropriate outcome to use as primary, and that we would examine other endpoints. All reviewers have argued that a more appropriate primary outcome would be the change from baseline in the mean CDRS-R score. I agree; when this outcome is examined in both studies, statistically significant superiority of

drug compared to placebo is obtained. Although one could argue that this post hoc choice of primary outcome is inappropriate (in addition to the fact that no adjustment of the alpha has been made for multiple comparisons), I agree with the review staff that this is the appropriate outcome to examine, and that, for all intents and purposes, we had informed the sponsor of this prior to the analyses of these studies.

Study HCJE also had additional phases beyond the acute phase. These phases included a randomized extension, in which non-responders to fluoxetine were randomized to the same or higher doses and placebo patients continued on placebo, and an additional long-term phase, in which responders to fluoxetine were re-randomized to drug or placebo. Dr. Shen, in her review (page 26) suggests that the analyses of these phases may not be appropriate, and I agree. For these reasons, these results will not be considered further.

As Drs. Mosholder and Shen have pointed out, in Study X065 there was a significant imbalance at baseline in the number of patients with co-morbid anxiety, with the fluoxetine group having more such patients. An analysis of the between-treatment difference on the mean change from baseline in CDRS-R in the group with co-morbid anxiety yielded a p-value of 0.0016, while a similar analysis of the group without co-morbid anxiety yielded a p-value of 0.11. The placebo group in the latter group was much greater than in the former group (N=34 and 13, respectively), and the placebo response in the group without anxiety was much greater than in the group with anxiety (change from baseline of –12.7 and –4.6, respectively); the change from baseline in both fluoxetine groups was nearly the same.

As Dr. Shen notes, an ANOVA in which baseline co-morbidity was included as a factor still gave a statistically significant result in favor of fluoxetine, and, as Dr. Mosholder, points out, there were clearly consistent results on the MADRS, a standard depression scale that might be less sensitive to any specific anxiolytic effects of fluoxetine. For these reasons, I believe that this imbalance does not invalidate the overall results.

A more troubling problem relates to the maintenance of the blind in this trial.

Specifically, as noted by Dr. Mosholder (page 19), there were several potential breeches in the blind, including access to the randomization code by a study nurse, knowledge of treatment assignment of 2 patients by a non-investigator physician, and knowledge of treatment assignment in "less than 10 patients" after they completed their participation in the study, but before the entire study was completed.

Of even more concern are reports that, according to Lilly, it was not uncommon for treatment assignment (or even plasma levels of drug) to be seen in patient records. According to Dr. Mosholder, Eli Lilly contends that these data were

typically added after completion of the study, and that, "...very rarely did the team see evidence the site did, in fact, unblind the patient's assigned therapy...".

As it turns out, the Agency has not performed its own inspection of this study, and, given the indications of potential blind-breaking, I believe we should conduct our own inspection prior to approving the application.

Obsessive Compulsive Disorder (OCD)

The sponsor has conducted a single, multi-center, randomized placebo controlled trial in pediatric patients (ages 7-17) with OCD. Patients were treated for 13 weeks, and could be titrated to between 20-60 mg/day after week 4. The primary outcome measure was the change from baseline in mean CYBOCS score. The p-value for the primary contrast was 0.026, with similar results obtained for several secondary, global measures.

About equal numbers of patients received 20 mg (N=35) and doses greater than 20 mg (40 mg, N=16; 60 mg, N=15).

Pharmacokinetics

As noted by the review team, a 20 mg dose of fluoxetine in children resulted in plasma levels of fluoxetine about twice those seen in adolescents given a 20 mg dose. However, when corrected for weight, the levels were about the same, and about the same as seen in adults after a 20 mg dose.

Safety

There was no important safety signal seen in these patients not previously seen in adults (although the experience is relatively small, N=250 patients treated with drug, with the maximum dose in almost all patients being 20 mg), with the exception of 2 issues.

After 19 weeks of treatment in Study HCJE, one analysis of EKG interval data revealed a non-trivial mean increase in QTc duration (approximately 7 msec increase compared to placebo). The sponsor performed 2 additional analyses, including one in which the EKGs were read by computer, which did not reveal this increase. Because the sponsor did not explain why the latter analyses should be considered preferable, we will ask for a further explanation of this finding.

Finally, there was a statistically significant decreased gain in height and weight compared to placebo at Week 19 of Study HCJE (see Dr. Mosholder's review, page 23). While numerically small, this finding is of concern.

The finding takes on increased importance in light of a finding of statistically

significant decreases in alkaline phosphatase compared to placebo at Week 19 in Study HCJE, which may reflect disordered bone development. These differences were also seen in the relapse prevention phase. We will ask the sponsor to further address the effects of fluoxetine treatment on growth and development.

COMMENTS

The sponsor has presented the results of 2 controlled trials in patients with MDD, and the results of 1 controlled trial in patients with OCD. These studies support the conclusion that fluoxetine is effective treatment for each of these indications in pediatric patients, with one caveat. Because of the possibility that there was a break in the blind in Study X-065 that could affect our interpretation of it as a study contributing to a finding of substantial evidence of effectiveness, I believe that the Agency must inspect this study before the application can be approved.

The sponsor has submitted sufficient experience for us to conclude that at least short-term use of 20 mg/day of fluoxetine in the pediatric population is relatively well tolerated, although, as I have noted, we will ask the sponsor to further address the issues of QTc prolongation, and decreased gain in height and weight. The experience at doses greater than 20 mg/day is minimal.

Given these considerations, I consider the application approvable.

The one remaining issue that needs to be addressed, in my view, is the dosing regimen to be recommended in labeling.

As described, in the MDD studies, a dose of 20 mg/day was studied. In the OCD study, a dose range of 20-60 mg/day was studied. In all studies, a dose of 10 mg/day was first given, for varying durations. As has also been discussed, children achieve plasma levels of parent drug about twice those achieved with the same dose (actually, kinetic data are available only for the 20 mg dose) given to adolescents and adults. However, when corrected for weight, the levels are about the same. These facts raise a question about the appropriate dose to recommend in the pediatric population.

One could simply recommend in labeling the doses studied in the particular indications. That is, a maintenance dose of 20 mg/day for pediatric patients with MDD, and a range of 20-60 mg/day in pediatric patients with OCD (in this latter condition, we cannot tell, empirically from the trial, which dose in this range is effective). Further, with regard to OCD, there is very little safety data in pediatric patients at daily doses greater than 20 mg; if we believed that doses greater than 20 mg should be recommended, based on the controlled trials, there would be inadequate evidence to support the safety of these doses. However, we know that children (more accurately, low weight patients, who are much more likely to

be children) at these doses will be exposed to about twice the circulating fluoxetine levels that adolescents will be exposed to.

One could argue that, given this latter fact, we should recommend only the lower doses in children (again, more accurately lower weight patients), on the theory that we know that the plasma levels achieved in adolescents and adults at a 20 mg dose are associated with effectiveness, and that we therefore can conclude that it is these plasma levels we should try to achieve in children, and these levels can only be achieved by lowering the dose in children relative to that recommended for adolescents. To recommend the higher doses in children would be inappropriate, because it would expose them to unnecessarily high plasma levels.

There is a problem associated with this latter approach. This approach requires extrapolating (regarding effectiveness) from plasma levels we believe to be "effective" in adolescents and adults to children (it also requires that we know something about an effective plasma range for a specific indication; while we strictly do not have this information, I do not believe it is absolutely critical for my argument). Specifically, this approach requires that we assume that the plasma levels seen at an effective dose in adults and adolescents are the plasma levels associated with effectiveness in children.

Unfortunately, we do not have empirical data that establishes this fact. In particular, we know from the trials presented in this application that 20 mg/day is an effective dose in children (and adolescents) with MDD, and 20-60 mg/day is an effective dose range in children (and adolescents) with OCD. We also know that smaller patients (i.e., children) were, in general, exposed to considerably greater levels of fluoxetine at these doses than were adolescents (and adults). We do **not** know, however, whether or not children ***need*** these higher levels for the drug to be effective (one could certainly imagine that this might be so), and, therefore, we cannot know that recommending a lower dose in children, a maneuver designed to achieve the same plasma levels as in adolescents, is appropriate.

This is less of problem with the MDD indication than it is for the OCD indication.

Because we have sufficient safety data in children at a dose of 20 mg/day, we could recommend this dose in patients with MDD, since this is the dose shown to be effective. While recommending this dose **might** subject children to levels greater than they need (again, we do not know this is true), at least we have some confidence that these levels are, in general, reasonably well tolerated (and, again, they may be needed).

In OCD, though, we do not know that a dose of 20 mg/day is effective, only that the range of 20-60 mg/day is effective. As noted above, though, we do not have sufficient safety experience at doses greater than 20 mg/day in children (or

adolescents) to comfortably recommend these higher doses. However, there is one factor that supports recommending the lower 20 mg dose in children with OCD.

OCD is generally accepted to begin, in most cases, in childhood (unlike MDD). For this reason, it is reasonable to consider that OCD in pediatric patients is more similar to OCD in adults than is, for example, MDD (though it has not been established that pediatric OCD is **identical** to adult OCD; if it were, we might not require a controlled trial in pediatric patients). Indeed, our belief that pediatric OCD is more like adult OCD, and that this is differenct for MDD, is operationalized in our policy that to gain a pediatric OCD claim only one controlled trial is needed, while 2 such trials are needed to gain a claim for pediatric MDD when the drug is approved for adult MDD.

In addition, while we do not know with certainty that 20 mg is effective in pediatric OCD, we do know that 20 mg is an effective dose in adults, and it is in the range shown to be effective in pediatric OCD (indeed, half the patients in the study received this as a maintenance dose).

Further, we know that the plasma levels associated with an effective dose (20 mg) in adults with MDD are the same as those associated with the effective dose (which is 20 mg) in adolescents, lending credence to the idea that the same plasma levels are effective in adolescents and adults for at least one disease, a disease, as I noted above, for which we have less reason to accept its similarity between adults and adolescents than we do for OCD.

Given that the same plasma levels are effective in adults and adolescents for MDD, it is reasonable, in my view, to conclude, given the results of the study in OCD, that this same principle holds for OCD. This suggests that the 20 mg dose is effective in adolescents, at least, with OCD (since that dose gives the same plasma levels in both adults and adolescents, and these levels are associated with effectiveness in adults). While, again, we have no empirical evidence that it is effective in children, if we accept 1) that this dose is effective in adolescents, 2) the similarities of OCD across age groups, and 3) the presumption that the same dose (i.e., 20 mg/day) is effective in children, adolescents, and adults with MDD, then it is not unreasonable, in my view, to conclude that 20 mg is an effective dose in children with OCD. Further, while it entails additional assumptions, it is again not unreasonable in my view to further conclude that the same relationship that holds for dose also holds for the "effective" plasma range across all age groups. For this reason, it is acceptable to offer dosing recommendations in labeling for children with OCD that focuses on the 20 mg/day (or lower) dose.

The proposed dosing recommendations in the version of labeling we will send to the sponsor embodies these principles. Specifically, for MDD, the label states that the recommended dose in low weight children may be 10 mg/day, but that the dose can be increased to 20 mg/day.

For OCD, labeling recommends that the initial dose be 10 mg/day for lower weight children, and that additional increases can be considered if response is not adequate. The recommended dose range is 20-30 mg/day, and our version states that experience with doses greater than 20 mg is limited, and that there is no experience with daily doses greater than 60 mg.

For the reasons stated above, then, I will issue the attached Approvable letter, with appended draft labeling.

Russell Katz, M.D.

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/s/

Russell Katz
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MEDICAL OFFICER

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 3, 2001

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for
the Prozac (fluoxetine) Pediatric Use Supplement

TO: File NDA 18-936/S-064
[**Note:** This overview should be filed with the 9-14-00
original submission.]

1.0 BACKGROUND

Prozac (fluoxetine) is an SSRI currently approved for treating depression, OCD, and bulimia in adults. This labeling supplement is intended to support labeling language to extend the use of Prozac into the pediatric age group in the treatment of depression and OCD. At the present time, no drugs are specifically indicated for the treatment of depression in pediatric patients. Three drugs (Anafranil, Luvox, and Zoloft) include labeling language to support the treatment of OCD in pediatric patients.

Lilly sponsored three of the four studies in support of this supplement, i.e., HCJE in depression, HCJW in OCD, and a PK study (HCIU). The fourth study, X065, was conducted by Emslie and the data were obtained by Lilly.

This supplement was submitted in response to a Written Request issued on 4-12-99. Based on this supplement, Lilly was granted pediatric exclusivity by CDER's Pediatric Exclusivity Board on 11-15-00.

An earlier supplement [redacted] also sought to support labeling language for the use of Prozac in pediatric depression and OCD. That supplement provided only the published paper regarding the Emslie study in support of the depression claim. We rejected this claim, arguing that, given the preponderance of negative studies in pediatric depression, one cannot easily extrapolate from adult data. Thus, we asked for a second study. In addition, we asked that the actual data from the Emslie study be submitted so that we could confirm the analyses.

In addition, we also noted that we would have needed the complete data for this study in order to complete our review. We did, however, acknowledge that for OCD we would accept a single positive study in support of an OCD claim in pediatrics.

Dr. Andrew Mosholder from the Psychopharmacology Group has reviewed this supplement, and I refer to his 6-25-01 review for additional details of the submitted data. The efficacy data have also been reviewed by Yuan-li Shen, Ph.D., from the Biometrics Group.

2.0 DEPRESSION CLAIM

As noted, results from 2 depression studies were provided in support of the depression claim, i.e., study HCJE and X065 (Emslie).

2.1 Study HCJE

Acute Phase

This was a randomized, double-blind, 9-week, parallel group, 22-center US study comparing fluoxetine vs placebo in children and adolescents (ages 8-17) meeting DSM-IV criteria for MDD. The randomization was 1:1 for fluoxetine vs placebo. The primary efficacy assessment was the children's CDRS-R, and the protocol specified primary outcome was the proportion of patients achieving $\geq$ 30% reduction in their CDRS-R score at endpoint compared to baseline. Dosing began at 10 mg/day for 1 week, then 20 mg/day for 8 weeks.

A total of n=219 patients were randomized, including 109 to fluoxetine and 110 to placebo. There were slightly more children (n=122) than adolescents (n=97). The sample was roughly equally distributed regarding gender, and was predominantly Caucasian. Eighty-three percent of fluoxetine patients completed the 9-week study, compared to 62% of placebo patients.

For fluoxetine, the proportion of patients achieving $\geq$ 30% reduction in their CDRS-R score at endpoint compared to baseline was 65% compared to 54% for placebo (p=0.09). Thus, this study failed on the protocol specified primary endpoint. On the other hand, the mean change from baseline on CDRS-R was -22.0 for fluoxetine vs -14.9 for placebo ($p< 0.001$). There was no treatment X age or treatment X gender effects for this outcome. Fluoxetine was also superior to placebo on mean change from baseline for CGI-Severity and MADRS scores, and on the CGI-I response criterion (final score of 1 or 2). It is also worth noting that in a 4-12-99 letter we informed the sponsor that we did not consider Lilly's primary outcome ($\geq$ 30% reduction in CDRS-R) to be optimal, and indicated that we would be looking at other measures as well. Thus, it would not be unreasonable, in my view, to consider change from baseline on the CDRS-R as the critical measure in this study.

Long-Term Phase

At the end of 9 weeks, the plan was for responders on fluoxetine to continue on 20 mg, while nonresponders on fluoxetine were to be randomized to either continuation on fluoxetine 20 mg or titration in a range of 40-60 mg/day. Placebo patients were to continue on placebo, presumably regardless of responder/nonresponder status. This phase was to last 10 weeks.

Finally, there was to be an 8-month relapse prevention phase, during which responders on fluoxetine (at any dose) were to be randomized to continuation on fluoxetine or placebo, with observation for relapse (CDRS-R score > 40, plus 2 weeks of "clinical deterioration").

n=29 fluoxetine nonresponders were randomized during the initial 10 week LT phase, with 71% of those getting the higher dose converting to responder status vs 33% of those continuing on fluoxetine 20 mg (p=0.13). After 19 weeks, there were a total of n=40 fluoxetine responders who were randomized for the relapse prevention phase (n=20 for each of the 2 groups). Using time to relapse as the primary analysis, fluoxetine was favored over placebo (p=0.046). However, Dr. Shen has argued that this is not a robust finding. A worst-case analysis that takes into consideration all early withdrawals to represent relapse results in a non-significant p-value (p=0.267).

Comment: While the acute phase of this study did not succeed on the protocol specified primary outcome, the results on other outcomes that we actually prefer are very strong. Thus, I agree with Dr. Mosholder that the acute phase of this study can be considered a positive study for pediatric depression. The relapse prevention phase of this study involves a very small number of patients, and is apparently not robust to an alternative analysis. On the other hand, the p-value for the primary outcome in this study is significant. While I think we need further discussion on this point, there is no need to reach a final judgement on the long-term data before taking an approvable action, since the sponsor did not propose any labeling language pertinent to long-term use in their proposed labeling.

2.2 Study X065 (Emslie)

This was a randomized, double-blind, 8-week, parallel group, single-center US study comparing fluoxetine 20 mg vs placebo in children and adolescents (ages 8-17) meeting DSM-III-R criteria for MDD. The randomization was 1:1 for fluoxetine vs placebo. The primary efficacy assessment was the children's CDRS-R, and the primary outcome selected by Lilly, prior to breaking the blind, was the proportion of patients achieving ≥ 30% reduction in their CDRS-R score at endpoint compared to baseline. This was different than the primary endpoint specified in the grant proposal for this study, i.e., the proportion of completing subjects who recover, where recovery was defined as a CDRS-R score < 28 and a CGI-I of 1 or 2. It is also worth noting that in a 4-12-99 letter we informed the sponsor that we did not consider Lilly's primary outcome (≥ 30% reduction in CDRS-R) to be optimal, and indicated that we would be looking at other measures as well. Thus, it would not be unreasonable, in my view, to consider change from baseline on the CDRS-R as the critical measure in this study. Dosing apparently began at 20 mg/day for those assigned to fluoxetine, and continued at that dose for 8 weeks.

A total of n=96 patients were randomized, including 48 to fluoxetine and 48 to placebo. There were identical numbers of children (n=48) and adolescents (n=48). The sample was roughly equally

distributed regarding gender, and was predominantly Caucasian. Sixty-nine percent of fluoxetine and 52% of placebo patients completed the 8-week study.

For fluoxetine, the proportion of patients achieving $\geq$ 30% reduction in their CDRS-R score at endpoint compared to baseline was 58% compared to 32% for placebo (p=0.013). Results were not significant for the grant proposal specified endpoint (fluoxetine 29% vs placebo 19%, p=0.339). The mean change from baseline (LOCF) on CDRS-R was -20.2 for fluoxetine vs -10.5 for placebo (p=0.002). Fluoxetine was also favored over placebo on CGI-Improvement (p=0.040). There was no treatment X age or treatment X gender effect for these outcomes.

Drs. Mosholder and Shen note that there was an imbalance at baseline in the proportion of patients with comorbid anxiety disorders, with the fluoxetine group having an excess of such patients. Subgroup analyses based on presence or absence of comorbid anxiety disorders revealed a greater fluoxetine/placebo separation in the responder and change from baseline analyses in the subgroup with comorbid anxiety disorders compared to those without. While statistical significance is maintained only in the subgroup with comorbid anxiety disorders, it is true that fluoxetine is numerically favored over placebo in both subgroups, and the p-value for the change from baseline analysis in the subgroup without comorbid anxiety disorders is at least trending in favor of fluoxetine (p=0.11). There were also other problems noted, in particular the potential for unblinding due to the method used for formulating the placebo and the possibility of unblinding of a few patients due to knowledge of the code.

Comment: There were some problems with this study regarding specification of a primary outcome, imbalance of groups on comorbid anxiety, and the potential for minimal unblinding. However, I agree with Dr. Mosholder that these problems do not overcome the fairly robust outcome on change from baseline in the CDRS-R, the symptom measure that we consider optimal for this population. Positive outcomes on other measures support the positive finding for mean change from baseline. The subgroup differences based on presense or absence of comorbid anxiety disorders are interesting, but not of sufficient concern, in my view, to invalidate the overall positive results. Thus, I consider this a second positive study.

2.3 Conclusions Regarding Antidepressant Efficacy

Overall, I consider studies HCJE and X-065 (Emslie) positive studies with regard to the short-term efficacy of fluoxetine in major depressive disorder in pediatric patients. Given the results of the PK studies showing plasma levels in smaller weight children roughly twice those seen in adolescents receiving the same 20 mg dose, a dose that was effective in both children and adolescents, it seems reasonable to suggest that a dose of 10 mg may be sufficient in lower weight children.

3.0 OBSESSIVE COMPULSIVE DISORDER CLAIM

The OCD claim is based on study HCJW. This was a randomized, double-blind, 13-week, parallel group, 22-center US study comparing fluoxetine vs placebo in children and adolescents (ages 7 to 17) meeting DSM-IV criteria for OCD. The randomization was 2:1 for fluoxetine vs placebo. The

primary efficacy assessment was the children's YBOCS (CYBOCS), and the protocol specified primary outcome was change from baseline to endpoint in CYBOCS. Dosing began at 10 mg/day for 2 weeks, then 20 mg/day for 2 weeks, and then titration in a range of 20-60 mg/day, as needed. A total of n=103 patients were randomized, including 71 to fluoxetine and 32 to placebo. There were more children (n=75) than adolescents (n=28). The sample was roughly equally distributed regarding gender, and was predominantly Caucasian. Roughly 2/3 of patients completed the 13-week study. The final doses for the n=71 fluoxetine-treated patients were as follows:

10 mg--5
20 mg--35
40 mg--16
60 mg--15

The mean change from baseline on CYBOCS was -9.5 for fluoxetine vs -5.2 for placebo (p=0.026). There were no treatment X age or treatment X gender effects for this outcome. Fluoxetine was also superior to placebo on CGI-severity and the NIMH global OCD scale.

Comment: Both Drs. Mosholder and Shen concluded that this study provides evidence for the effectiveness of fluoxetine in the treatment of pediatric OCD, and I agree. Dr. Mosholder has recommended a maximum fluoxetine dose of 20 mg, based on his concern that there are no PK data for doses higher than 20 mg/day, and the total systematic experience with doses greater than 20 mg/day comes from a total sample of n=31 patients. Regarding the PK data, OCPB has suggested that, given the similar PK in adults and children based on the data that are available in this program, the information provided is sufficient to support the approval of this supplement at the recommended doses, i.e., up to 60 mg/day. While I agree with this position, I feel that, as with the depression claim, we can scale down the recommended dosing range for smaller children, based on the weight related differences in observed plasma levels. Thus, the recommended dosing range in smaller children with OCD would be 10-30 mg/day.

4.0 PHARMACOKINETIC DATA

PK data were available from studies HCIU and HCJE. Children in these studies had average steady-state fluoxetine and norfluoxetine plasma concentrations that were 2 and 1.5 fold greater than those observed in adolescents, differences that could be attributed virtually entirely to differences in body weight. The adolescent levels were comparable to those observed in adults given a 20 mg dose. PK parameters were all comparable in children and adolescents. The OCPB has recommended that these data are sufficient to support the sponsor's proposed dosing recommendations, i.e., up to 60 mg/day for OCD. Following discussion in the biopharmaceutics briefing, there was general agreement that it would not be unreasonable to recommend dosing in lower weight children roughly half that in adolescents and adults, given the weight related differences in plasma exposure that would be anticipated, along with the finding of apparently equivalent efficacy at the 20 mg dose in children and adolescents.

5.0 SAFETY DATA

The safety database for this supplement included a total of n=250 patients exposed to fluoxetine and n=190 exposed to placebo. The mean age was 12 (range: 6-18), with a roughly equal gender distribution. Of a total exposure person-time (this was provided only for the acute phase for the 3 placebo-controlled trials) of roughly 44 years, 34 years involved dosing at 20 mg/day. The remaining person-time was distributed as follows:

10 mg/day	5 PY
40 mg/day	3 PY
60 mg/day	2 PY

Only n=31 patients received doses above 20 mg/day.

Dr. Mosholder has provided a complete review of the safety findings. Overall, the safety profile for fluoxetine in the pediatric population was similar to that observed in adults. However, the following findings are of particular note:

-For the baseline to 19 week comparison in HCJE, there was a statistically significant greater mean decrease in alkaline phosphatase from baseline to 19 weeks in the fluoxetine group vs placebo (-35 vs -5). For the baseline to 51 week comparison in HCJE, there was a statistically significant greater mean decrease in alkaline phosphatase from baseline to 51 weeks in the fluoxetine group vs placebo (-39 vs -5;).

-For the baseline to 19 week comparison in HCJE, there was a statistically significant lesser mean increase in height and weight from baseline to 19 weeks in the fluoxetine group vs placebo:

Group	Fluoxetine	Placebo
Mean change in height (cm)	+1.0	+2.0
Mean change in weight (kg)	+1.2	+2.3

-For the baseline to 51 week comparison in HCJE, there was a lesser mean increase in height from baseline to 51 weeks in the fluoxetine group vs placebo (+2.9 vs +5.1 cm; p=0.065)

-An initial analysis of QTc (cube root corrected) data for the baseline to 19 week comparison in HCJE, there was a statistically significant greater increase of 7.4 msec for fluoxetine vs 0.2 msec for placebo. Subsequent re-analyses by 2 different consulting groups contracted by Lilly yielded no statistically significant differences. QTc data from the PK study (HCIU), as analyzed by . ——— ——— actually showed a decrease for fluoxetine vs placebo.

-For the 3 placebo-controlled trials, there was a 2.6% 6/228 risk of mania for fluoxetine vs 0% for placebo (p=0.034). Four of these 6 patients discontinued due to mania.

Comment:

-The findings of reduced growth velocity (both height and weight), along with reduced alkaline phosphatase, are important, and I agree with Dr. Mosholder's proposal to add this information to

labeling. I also agree that we should ask the sponsor to re-analyze these data using age and gender adjusted height and weight percentiles; in fact, this should be done prior to final approval.

-The discrepant QTc results, depending on which consultant was used, need explanation. Dr. Mosholder has proposed adding the results of the initial analysis; however, my preference would be to ask the sponsor to provide a better rationale for why we should accept the results of the later analyses. I do agree that a PK/PD study is needed to better understand whether or not there is a QTc effect of fluoxetine in pediatric patients. However, given the lack of a postmarketing signal for an important QTc effect of this drug, I think this could be a phase 4 request.

-Dr. Mosholder has suggested that doses of fluoxetine above 20 mg not be approved, given the limited systematic safety experience at higher doses and the lack of any PK data at higher doses. The difficulty with this suggestion is that it would not permit adding a claim for OCD in this population, since patients in study HCJW were dosed in a range of 20-60 mg/day. Indeed, 31 of the 71 patients receiving fluoxetine in that trial received doses greater than 20 mg/day. I think a reasonable alternative would be to rely on a lack a safety signal in postmarketing data, if it can be determined that there has been substantial use of fluoxetine in pediatric patients at doses in the 40-60 mg/day range. An updated literature review might also be helpful in this regard. In addition, as noted earlier, I think it would be reasonable to recommend dosing in a range of 10-30 mg/day for lower weight children with OCD, based purely on PK data, i.e., the weight related differences in exposure between children and adolescents.

6.0 CONCLUSIONS AND RECOMMENDATIONS

In my view, the sponsor has provided sufficient data to support the approvablity of fluoxetine in the treatment of MDD and OCD in pediatric patients, including both children and adolescents. However, I recommend the following be requested prior to our taking a final action:

-The findings on reduced growth velocity for height and weight, along with the reduced levels of alkaline phosphatase, need to be included prominently in labeling. We should ask the sponsor to re-analyze these data using age and gender adjusted height and weight percentiles prior to final approval.

-The discrepant QTc results, depending on which consultant was used, need explanation. We need to ask the sponsor to provide a better rationale for why we should accept the results of the later analyses. We can ask for a PK/PD study to better understand whether or not there is a QTc effect of fluoxetine in pediatric patients as a phase 4 commitment.

In the meantime, I recommend that we issue the drafted approvable letter, along with our proposed labeling, in anticipation of final approval.

cc:
Orig NDA 18-936/S-064
HFD-120
HFD-120/TLaughren/RKatz/AMosholder/PDavid

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
7/3/01 08:53:49 AM
MEDICAL OFFICER

MEMO OF TELEPHONE CALL

Date:	November 15, 2000
NDA:	18-936/SE5-064
Subject:	Pediatric Patent Exclusivity Granted
Drug:	Prozac (fluoxetine HCl) Pulvules
Indication:	Pediatric Depression and OCD
Firm:	Lilly
Contact:	Dave Johnson, Ph.D., Drug Regulatory Affairs
Phone #:	(317) 256-6408
Fax #:	(317) 276-1652

I contacted Dr. Johnson in reference to Lilly's pediatric efficacy supplement dated September 14, 2000. Reference was also made to an Agency pediatric written request letter dated April 12, 1999, and subsequently amended on May 19, 1999, and February 29, 2000.

I informed Dr. Johnson that the Pediatric Exclusivity Board had convened to discuss whether this supplemental application had met the terms of the written request, as amended, and pediatric exclusivity was to be granted.

I concluded the conversation bet stating that the additional exclusivity of Prozac would be posted in the electronic Orange Book within the new couple of days.

Dr. Johnson thanked me for the telephone call.

Paul A. David, R.Ph.
Regulatory Project Manager

NDA: ORIG 18-936/SE5-064
NDA: DIV FILE
HFD-120/R.Katz/T.Laughren
HFD-120/A.Mosholder
HFD-120/P.David

MEMO OF TELEPHONE CALL

/s/

Paul David
11/17/00 09:04:20 AM
CSO