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: May 6, 2008

FROM: Thomas P. Laughren, M.D.
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HFD-130

SUBJECT: Recommendation for approval action for this supplement in support of a maintenance claim for Strattera (atomoxetine) in the treatment of ADHD.

TO: File NDA 21-411/S-005 (This memo should be filed with the 11-14-07 submission in response to our 4-20-07 not approvable letter.)

Background

Strattera is approved for the treatment of ADHD in adults and pediatric patients, based on positive short-term trials. This supplement was submitted 3-15-04 and was in support of language in labeling describing a maintenance study in children and adolescents with ADHD (LYAF). This was a randomized withdrawal study involving an initial randomization of responders after a 10-week open label period during which patients were in a responder status for an average of about 4 weeks. There was also a second randomization of atomoxetine responders after a period approximately 38 weeks. In fact, the primary analysis for the first randomization was significant (p=0.013; mean time to relapse was 227 days for drug and 158 days for placebo; relapse rates were 21% for drug and 37% for placebo). The primary analysis for the second randomization was also essentially significant (p=0.055; mean time to relapse was 160 days for drug and 132 days for placebo; relapse rates were 5% for drug and 15% for placebo). Nevertheless, the agency issued an approvable letter on 1-14-05, in which it asked Lilly to consider reanalyzing the data for a subgroup of patients who were responders for at least 8 weeks before randomization. We met with Lilly to consider their plans for this reanalysis on 9-1-05, and they resubmitted the application on 10-24-06.

The statistical and clinical teams did not consider the data from this resubmission sufficient to support a claim for a treatment effect based on time to relapse after the first randomization. First, they noted that the result based on the re-analysis subgroup proposed in the approvable letter, i.e, without allowance for excursions, was not statistically significant (p=0.16). Although the sponsor's re-analysis based on their preferred post-hoc excursion rule yielded a nominally statistically significant result (p=0.016), it was but one of many possible such rules. Thus, they felt that we should not accept the p-value associated with this single rule at face value without looking at other possible excursion rules (i.e., sensitivity analyses). I generally agree that such analyses are critical in this situation where the proposed excursion rule was established post hoc.

In exploring other possible rules, we found that the result was not robust to slight changes in this post-hoc rule for selecting the subgroup for reanalysis. While it is true that FDA's recommendation to analyze the subgroup that responded for at least 8 weeks was also post-hoc, it was proposed without having looked at the data as a clinically meaningful alternative and as a potential approach to salvaging a study that otherwise had been viewed by the clinical team in place at that time as a failure.

The lack of robustness of the p-value for the treatment difference in time to relapse in the subgroup of patients that responded at least between visits 6 and 11 continuously, except for the possibility of excursions at up to two visits, was illustrated by the following points. [Note: Our p-values were slightly different than the sponsor's, because we had excluded data for 3 patients for whom ADHDRS data were missing. Even if these patients were included, however, the results would not have materially changed.]

- If only one CGIS=3 excursion is permitted, rather than two as the sponsor proposed, p=0.066.
- The original criteria for a response were at least a 25% decrease on the ADHDRS from baseline and a CGIS < 3. Since the original criteria for response depend on both the CGIS and the ADHDRS, it is not clear why the excursion rule chosen by the sponsor permited a slight weakening of the response criterion for the CGIS but not for the ADHDRS. It might be reasonable to call a CGIS score of 3 and/or an ADHDRS score between a 22% and a 25% decrease from baseline an excursion. For a subgroup of patients that responded between visit 6 and visit 11 permitting up to two excursions according to this slightly different definition for excursions yielded a p-value of 0.080. When we weakened the ADHDRS criteria slightly more by permitting an ADHDRS score representing a decrease of between 17% and 25% from the baseline score to be an excursion, the result was p=0.097.

The clinical and statistical teams felt that a claim of effect on time to relapse following the second randomization was also not possible because it was contingent on demonstrating statistical significance of the effect on time to relapse after the first randomization, which had not been clearly and consistently demonstrated, in their view. Therefore, they did not consider the efficacy results from this trial to be persuasive to support a maintenance claim.

While I generally agreed with this conclusion, I thought it was a close call, and likely to be controversial. First, as I have noted, the sponsor's originally planned analysis was positive, and it was our objection to the very short time in "responder" status that led to the re-analyses. It's true that we are now informing sponsors that we expect patients in these trials to be in a "responder" status for a meaningful period of time, but we clearly had not provided that advice at the time the protocol was submitted. Second, the results for some of the sensitivity analyses for the first randomization, while not significant, were at least trending in the direction of significance. The results for the second randomization were quite robust, including almost all of the sensitivity analyses. Rejecting these analyses for the second randomization hinges entirely on the argument that the sponsor was not entitled to look at these data since the first randomization was, in our view, not positive. In any case, we issued a non-approvable letter for this supplement on 4-20-07.

We met with the sponsor on 8-16-07 to further consider the usefulness of study LYAF to support a maintenance claim for ADHD. We established that we would not likely reach agreement on the various reanalyses that had been proposed, but in addition, we raised another issue that had not been previously discussed. We noted the finding from study LYAF that the mean time to relapse for patients assigned to placebo after the initial randomization was 158 days. We suggested that these findings seemed inconsistent with the nature of this illness. We raised the possibility that these findings might be conditioned upon where study LYAF was conducted, i.e., outside the US. The sponsor argued that these findings were not that unusual, and they identified 2 alternative sources of evidence, i.e., the Gillberg study and Lilly study HFBE. They suggested that the placebo survival curves in these studies were not unlike that in study LYAF. They also suggested that this finding was partly an artifact of the severe definition of relapse that required meeting criteria at 2 consecutive visits. They proposed resubmitting the application with more complete data on other maintenance studies in ADHD and also with alternative analyses using different definitions of relapse. We agreed to consider such a resubmission.

11-14-07 Resubmission of S-005

Placebo Relapse Data from Alternative Sources

Lilly Study HFBE: This was another Lilly-sponsored randomized withdrawal study similar in design to LYAF that was conducted in the US. It was a considerably smaller study and did not achieve a statistically significant outcome favoring atomoxetine. However, Lilly has demonstrated that the placebo survival curve from this study is essentially superimposable on the placebo survival curve from study LYAF. Thus, data from this study do support Lilly's argument that the placebo survival data observed in study LYAF are not idiosyncratic.

Gillberg Study: This was a Swedish randomized withdrawal study involving ADHD patients treated with amphetamine on an open label basis for 3 months. Responders were randomized to continuation on amphetamine or switch to placebo, for 12 months of observation for relapse. Relapse rates at 12 months were 71% for placebo and 29% for amphetamine. As seen in study LYAF and HFBE, relapse on placebo was not immediate, but rather, gradual over a period of many months.

MTA Study: The MTA study sponsored by NIMH had a later phase during which patients were free to discontinue methylphenidate or continue, whatever they and their parents and caregivers felt was most appropriate. This phase provides some insight into the rate of relapse, and again, it suggests that relapse is gradual rather than immediate.

Exploratory Analyses Using Alternative Definitions of Relapse

The sponsor did provide results from study LYAF using alternative definitions of relapse. These analyses did suggest slightly different results depending on the particular definition of relapse, however, the mean days to relapse for placebo patients were still quite long for all analyses. These analyses yielded statistically significant results favoring atomoxetine over placebo for all 7 alternative definitions of relapse, for both the initial randomization and the second randomization.

Conclusions and Recommendations

Dr. Ni Khin, the clinical team leader for this supplement, has concluded that this supplement can be approved, based essentially on the positive finding for the initial randomization in study LYAF, and the sponsor's argument that the placebo relapse data for this study are not atypical for this condition. However, she recommends against accepting language for a positive finding regarding the second randomization because the p-value just misses statistical significance (p=0.055). She also suggests mentioning in labeling that the positive results are derived from a nonUS study and she recommends asking Lilly to conduct another randomized withdrawal study in the US.

I agree that Lilly has made a reasonable case that the placebo relapse data for this study are not atypical for this condition. I also agree that we should consider the positive finding for the initial randomization in study LYAF sufficient to support a maintenance claim for this drug in ADHD. However, I am also inclined to accept the finding from the second randomization as positive. I acknowledge that the p-value just misses the 0.05 level of significance. It's true that we have to draw the line somewhere, but I think there are other findings here that would argue in favor of accepting this as a positive result. First, we already have positive evidence from the initial randomization. Second, we asked the sponsor to conduct a number of alternative analyses of the data from the second randomization, and they were all consistently and robustly positive. I don't think we have a sufficient basis for rejecting this outcome from the second randomization in study LYAF as not supporting a longer-term claim. Rather, I think we have a number of reasons for believing it is true. For similar reasons, I am not inclined to require the sponsor to conduct an additional randomized withdrawal study.

We have now reached agreement with the sponsor on final labeling for this product, and I will issue an approval letter.

cc:
HFD-130/TLaughren/MMathis/NKhin/NHemingway

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/s/

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MEDICAL OFFICER