

LYAQ. In these 2 open label studies (LYAQ was another study in which atomoxetine was given in combination with fluoxetine to create phenotypic PMs; we have only summary data for this study), over 350 pediatric patients had EKGs measured at 1 hour post dose, and at trough. In this cohort, there were approximately 25 PMs (a combination of genotypic PMs, and those created by the addition of fluoxetine [Study LYAQ]). There were no important increases in QTc in this cohort, and there was no overall relationship to plasma levels in this cohort, although it appears as if a relationship might exist at the highest levels (1500 ng/ml, with only 6 data points). According to the sponsor, the vast majority of this experience was at or above the therapeutic dose (1.2 mg/kg/day). While it is true that Tmax is later in PMs than in EMs, a 1 hour post-dose measurement might be considered to be relatively close to one taken at a true Tmax in PMs (again, given that the primary signal giving rise to concern was seen not at Tmax in Study LYAE, we might not be particularly concerned about measurements at exactly Tmax in this case). No patient in this cohort (Studies LYBB and LYAQ) had a plasma level equal to or greater than 2000 ng/ml.

In a fax sent to the division on 8/1/02, the sponsor presented a scatter-plot of plasma levels vs change in QT duration at peak in the adult controlled trials. While they contend that there is no statistically significant relationship ($p=.138$), it appears that there may be a direct relationship between levels and QT prolongation for the higher levels (1500 ng/ml and greater) although there are very few data points at that level (5 above 1500 ng/ml).

In summary, then, there are what appear to be significant increases in QTc duration in a study examining EKG at 60 and 75 mg BID in a study in PM adults at Time 0, but no such increase at Time 12 post-dose in the 60 mg BID group (with a real, but smaller increase in the 75 mg BID group at Time 12 compared to the increase at Time 0 in this group). Further, there is a relationship between plasma levels and QTc prolongation at Time 0, 4, and 12 hours post-dose in this study; this relationship may be largely driven by the 75 mg BID data (a level greater than the maximum effective dose in adults, which is 60 mg BID).

In addition, the proportion of patients meeting outlier criteria in the entire pediatric database is somewhat greater in PMs than in EMs, and about twice as many PMs than EMs with normal EKGs at baseline had prolonged QTc durations at endpoint. A single rising dose study in adults up to 120 mg showed increases in QTc duration at 2 hours post dose in PMs, and a pooled analysis of single dose data at 120 mg showed increases in QTc interval at several timepoints post-dose. Finally, there appeared to be a possible relationship between plasma levels and QT prolongation (up to 10 msec) at the highest plasma levels (1500 ng/ml) in the adult controlled studies.

On the other hand, EKGs from controlled and uncontrolled trials in both adults and pediatric patients, and EMs and PMs, revealed no mean increases in QTc duration. In the adult controlled trials, no mean increases were seen when EKGs

were measured at "peak" plasma concentrations (presumably 1 hour post-dose). Further, over 300 pediatric patients had EKGs done at 1 hour post-dose and trough; there were no mean changes, and no overall relationship was noted between plasma level and QTc duration. In another study (LYAY) in which fluoxetine was added to atomoxetine to produce phenotypic PMs, no important QT changes were seen (although patients achieved plasma levels that were only 60-70% those in genotypic PMs in Study LYAE).

In addition, in the study in which single doses up to 120 mg showed QTc prolongation, assessment of the EKG during the multiple dose phase of the study did not.

While there are hints that atomoxetine might be capable of increasing the QT duration in PMs, the data are inconsistent, at best. The primary finding suggests that, if there is an effect, it occurs at C_{min}, but other data (including from the same study) suggest that this is not a consistent finding. Perhaps the most compelling data come from the 75 mg BID dose group in Study LYAE (a dose greater than the maximum effective dose of 60 mg BID). In this dose group, a number of the post-dose EKGs show QTc prolongation, in addition to the primary finding at Time 0 (including at Time 12).

This finding, and the appearance of a possible relationship between the higher plasma levels in the adult controlled trials and QTc duration (as well as a hint of such a relationship at the higher plasma levels at the 1 hour EKGs in the pediatric population), suggests that there may be a real QT prolonging effect at higher plasma levels (i.e., >1500 ng/ml), independent of metabolic status (while we would expect that these higher plasma levels would ordinarily be achieved only in PMs, it appears that not all PMs reach these levels). Unfortunately, there is very little data at these levels in the database. This, of course, suggests that only a fraction of the PMs who receive the drug will produce these higher levels of atomoxetine, but we do not have a precise estimate of what that fraction is, given the relatively few PMs in whom plasma levels were obtained (in the combined pediatric patients from Studies LYBB and LYAQ, 6 patients had levels of at least 1500 ng/ml, out of a total of about 25 PMs). If we take this estimate of "high plasma level PMs" (25% of PMs, assuming the patients with the highest plasma levels were, in fact, PMs), and consider that 10% of Caucasians are PMs, then about 2.5% of Caucasian pediatric patients would be expected to produce high plasma levels. This translates into a relatively large number of patients who might be exposed to these levels once the drug is marketed.

Mean levels in Study LYAE (the study from which the primary finding arises) at the 60 mg BID dose were almost 3000 ng/ml, while the mean levels at the 75 mg BID dose group were about 4000 ng/ml. In Study LYAY (the fluoxetine-atomoxetine study) the mean levels at the 75 mg atomoxetine dose were about 2800 ng/ml. I have not seen a systematic analysis of the plasma level-QTc duration data by individual patient in Study LYAY; as noted earlier, there is a

relationship between plasma level and QTc duration in Study LYAE, and it appears that most of the relationship is accounted for by levels above 1500 ng/ml.

For these reasons, then, I would recommend that the sponsor document the relationship between levels of about 1500 ng/ml or greater and QTc prolongation. While the sponsor may believe that they have documented that there is little to no relationship between QTc duration and plasma level in general, as I have noted: 1) there is little well documented experience at these higher levels, 2) the data are at least suggestive that these higher levels may be associated with prolongation of the QT interval, and 3) clearly, at least some percentage of PMs reach these levels at therapeutic doses. I am not prepared at this point to conclude that there is an important increase in QT duration at these higher levels, but I believe there is sufficient reason to require the sponsor to further address this question. They may feel that they have adequate data in hand to dismiss this concern; if so, this data should be presented. It would also be important for the sponsor to address the question of the proportion of patients who will reasonably be expected to achieve these levels at recommended doses. If the proportion of such patients is vanishingly small, additional data may not be necessary; if the numbers are relatively large, it might be prudent to obtain considerable additional QTc-plasma level data (my crude calculation from the combined LYBB and LYAQ data revealed a 2.5% incidence in the Caucasian population).

It should be pointed out that much of the data addressing the effects of the drug on the QT interval come from clinical pharmacology studies that compare on-drug QT to a placebo or other baseline value. In many cases, there is no concomitant control group, so any effects of, for example, increasing doses, has the potential to be confounded by time effects (although such effects are not expected with a high probability). Further, and critically, there are very few patients with plasma levels in the 1500 ng/ml and over range; indeed, the data that there may be a signal of QTc prolongation at these levels, while suggestive, is equivocal for just this reason, I believe. It is this paucity of data at these levels, coupled with the hint of a signal of QTc prolongation, that underlies my recommendation for obtaining more relevant data to address the question.

In addition, and importantly, there is very little data in PMs at a therapeutic dose for more than 6 months (13 for 6 months, 1 for 1 year). In addition, of course, we do not know how many patients treated for these durations in the database achieved the higher levels about which I am concerned. According to the sponsor in a telephone conversation of 8/1/02, they have considerably more long term PM data (? Numbers) that they intend to submit. I believe it will be important for the sponsor to address the question of the adequacy of the long-term database in the PM population (as well as in the high plasma level group).

Finally, there is the question of whether or not we should require physicians to determine a patient's metabolic status prior to treatment initiation. One could argue that, given the 10 fold increase in plasma levels in PMs compared to EMs, and the increased incidence in a number of ADR in PMs compared to EMs, we should require such testing without further consideration. Even if we were to make this decision, there are questions that we are not yet in a position to answer. For example, should the patient be genotyped, using a commercially available kit? Are these kits readily available and approved by the Agency? If we would require this, would we require a Risk Management Program, to ensure, as much as possible, that the testing would be done, or would language in the labeling be sufficient? Instead of genotyping, could the same purpose be served by giving the patient a test dose of atomoxetine, and measuring plasma levels? Is there a commercially available assay for atomoxetine, or would the sponsor be required to assay all samples?

While I am sympathetic to the view that some sort of testing should be performed, I am reluctant to require it at this time. I believe we should obtain the additional data I have asked for (QT data at appropriately high plasma levels, an assessment of the proportion of patients who will be expected to achieve these levels, and additional long-term safety data in PMs and at these higher plasma levels). I believe that when we have received and analyzed this additional data, we will be in a better position to decide whether or not we should set the precedent of requiring a determination of the patient's metabolic status.

Other issues

Scheduling

The Controlled Substances Staff (CSS) recommends that we await the completion of Study LYBO, which was designed to address their previously expressed concerns, before a scheduling recommendation can be made. The sponsor has been informed, at a meeting many months ago, that the CSS would want to see the results of this study before they could make a scheduling recommendation. Whether this must be scheduled prior to approval is a matter for discussion.

Pharmacology

Dr. Elayan has recommended that the sponsor perform a juvenile rat study, 2 in vitro genotoxicity studies, and a Segment II rat study, all in an attempt to evaluate the toxicity of a single impurity — in the drug product. Dr. Rosloff does not feel that the Segment II study needs to be done, consistent with a previous decision on this matter, made in 4/02 (briefly, at that time, it was decided that a repeat Segment II study would need to be performed if the rat study that had been done—with low levels of this impurity—yielded worrisome results). Since this

was not the case, Dr. Rosloff recommends that the sponsor commit to performing only the juvenile rat study and the genotoxicity studies. The attached letter incorporates these requests.

CMC

The Office of Compliance (OC) has issued a Withhold recommendation for the application, based on GMP deficiencies at one of the sponsor's drug product packaging sites (there is one additional drug product packaging site included in the application). As a result, Dr. Gill-Sangha has now recommended, in a revised memo dated 8/7/02, that the application be considered Not Approvable (consistent with ONDC policy). I have discussed this with Dr. Tom Oliver, chemistry team leader, who recognizes that this revised recommendation will not affect the division's recommendation (see below). In any case, the sponsor may be able to adequately address the deficiencies before approval, or, if not, we could ultimately approve the application with the single remaining acceptable drug product packaging site.

Recommendation

For the reasons stated above, then, I recommend that the attached Approvable letter, with appended draft labeling, be issued.

/S/

Russell Katz, M.D.

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this page is the manifestation of the electronic signature.**

/s/

Russell Katz
8/8/02 12:47:24 PM
MEDICAL OFFICER

MEMORANDUM

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

DATE: November 21, 2002

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

SUBJECT: Recommendation for Approval Action for
Strattera (atomoxetine) capsules for the treatment of attention deficit hyperactivity
disorder (ADHD)

TO: File NDA 21-411
[Note: This overview should be filed with the 9-26-02 response to our 8-12-02
approvable letter.]

We issued an approvable letter for this NDA on 8-12-02, including requests for (1) comment on several clinical issues, (2) CMC deficiencies, (3) dissolution specifications, (4) a regulatory status update, (5) a world literature update, (6) a safety update, (7) and a commitment to conduct certain genotoxicity tests postmarketing. In addition, we provided draft labeling.

Lilly responded on 9-26-02.

Clinical Issues

Concern About the Potential for QTc Prolongation

-Based on a possible signal for QTc prolongation at higher exposures with atomoxetine from a single study (LYAE) in the development program, we asked for additional information and analyses, especially for pediatric patients at higher exposures. These data were provided, and were reviewed by Jerry Boehm, M.D., from the safety group. He concluded that, within the currently recommended dose range, there is no evidence of QTc prolongation in pediatric PM's (either naturally occurring or converted EM's), and no evidence for a relationship between QTc prolongation and plasma atomoxetine level in pediatric PM's.

-The sponsor performed a simulation based on the target dose of 1.2 mg/kg, and predicted that only 3/100,00 PM's dosed at this level would exceed a plasma level of 2000 ng/ml. However, our own pharmacometric consultants estimated that 7% of PM subjects treated at 1.2 mg/kg would exceed 2000 ng/ml, and 42% of subjects treated at 1.4 mg/kg would exceed this level. At the same time, however,

they estimated that an 8-fold increase in atomoxetine plasma concentration would yield only a 4 msec increase in QTc.

-While it is unclear which simulation is closer to the truth, there seems to be little support for the view that atomoxetine is associated with clinically important QTc prolongation. Thus, the safety group has concluded that no QTc statement is needed in atomoxetine labeling, and I agree. They also agree with the sponsor's proposal to permit pediatric doses (in pediatric patients ≤ 70 kg) as high as 1.4 mg/kg (or 100 mg) in the D&A section of labeling, based on the fact that many such patients in these trials were actually dosed at these levels, without any ill effects. Nevertheless, we will make clear in labeling that the target recommended dose is 1.2 mg/kg.

-Comment: Thus, I agree that the QTc prolongation issue is resolved.

Long-Term Efficacy Data

-In the approvable letter, we asked for a commitment to conduct studies, postapproval, to explore the longer-term efficacy of atomoxetine in ADHD.

-In their 9-26-02 response, Lilly provided protocols for two longer-term trials that are currently ongoing. Study LYAF is a randomized withdrawal study, involving 10 weeks of open treatment with atomoxetine, in which responders to atomoxetine are then randomized to continued atomoxetine or to placebo, for a 9-month observation period for relapse. Study LYBI is a study comparing atomoxetine and methylphenidate; responders to atomoxetine will be randomized to either their optimal atomoxetine dose or to a lower dose (0.5 mg/kg), with observation for relapse. They expect both studies to be completed by the end of 2003.

-Comment: This is an acceptable response.

Longer-Term Effects on Growth

-In the approvable letter, we asked for a commitment to conduct studies, postapproval, to explore the longer-term effects of atomoxetine on growth, preferably in controlled trials. Based on data submitted in the NDA, we had added information regarding growth effects of atomoxetine as a Warning statement.

-Lilly disputed our statement in labeling characterizing the growth effects of atomoxetine. Dr. Boehm has reviewed their response. Although he agrees that the longer-term data are difficult to interpret regarding longer-term growth effects, he believes that the actual findings, suggesting that weight and height percentiles drop slightly, even though weight and height increase, should be noted in labeling. I agree, and we have now reached agreement with Lilly on how best to characterize these effects in labeling.

-Regarding the conduct of longer-term controlled trials to explore growth effects, Lilly argued that, given the well-established effectiveness of pharmacological treatments for ADHD, it would not be feasible to conduct a longer-term study with a non-pharmacological control arm. In addition, they argued that the approach they used in the NDA, i.e., comparing growth rates of individuals exposed to atomoxetine with normative data, is adequate for assessing the growth effects.

-Comment: As noted, we have reached agreement on how best to characterize the growth effects in labeling. I agree with Lilly that long-term trials including a non-drug group would not likely be possible.

Appendicitis

-In the approvable letter, we asked the sponsor to report spontaneous cases of appendicitis as 15-day reports, and they have agreed to this. This request was based on a slight excess of appendicitis cases in the NDA.

CMC Deficiencies

-The manufacturing site with problems has been dropped. It is my understanding that all other CMC deficiencies have been adequately addressed.

Dissolution Specifications

-Lilly has accepted our proposed dissolution specifications.
-We continue to reject the sponsor's view that atomoxetine should be considered a BCS 1 drug, since it does not meet the dissolution standard; this conclusion should be noted in the approval letter.

Regulatory Status Update

-Lilly has reported that atomoxetine is, as yet, not approved anywhere in the world. However, registration applications are pending in three other countries: Canada; Australia; and New Zealand.

World Literature Update

-Lilly's response to our request for a literature update included the full text for 23 articles not submitted with the original NDA, some with animal data and some with human data. Michael Davidson, M.D., medical director of the Strattera product team at Lilly, reviewed these articles, and gave the following warrant: "The result of this review is that these literature references do not reveal any important new safety information and the conclusions of the articles are consistent with the conclusions of the data presented in the original NDA." I scanned the titles of the articles and reviewed relevant summary information, and I agree with this conclusion.

Safety Update

-Dr. Boehm has reviewed Lilly's safety update and their update on long-term safety data for PM subjects. There were no new findings from these data that would impact on labeling.

Commitment to Conduct Certain Genotoxicity Tests Postmarketing

-Lilly has committed to conducting the tests we had requested in the approvable letter.

Draft Labeling

-We have reached agreement with Lilly on final labeling for this product, as of 11-21-02.

Conclusions/Recommendations:

-I believe that all outstanding issues have been resolved at this point, including agreement on final labeling. Thus, I recommend that we approve this NDA with mutually agreed upon final labeling.

cc:

Orig NDA 21-411

HFD-120

HFD-120/TLaughren/RKatz/JRacoosin/RGlass/JBoehm/AMHomonnay

HFD-101/RTemple

DOC: MMATXADD.AP1

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/s/

Thomas Laughren
11/21/02 01:25:13 PM
MEDICAL OFFICER

1-20-99: The main focus of this meeting was a more detailed discussion of what studies would be needed to support what claims. We generally emphasized the need to focus studies on the pediatric population, and to conduct short-term trials to support acute efficacy, and randomized withdrawal studies to support longer-term use. We also discussed what would be needed for the pharmacokinetic program and a juvenile animal study.

2-8-00: This meeting focused on: (1) the need for a sufficient number of PM's to be included in the program, (2) the PK program, (3) the overall planned safety exposure, and (4) the possibility of a priority review.

3-6-01: This meeting focused on: (1) the finding of a possible QTc effect in PM's in study LYAE; (2) the adequacy of PM exposures in the program; (3) the adequacy of a single QD dosing study to support QD dosing; and (4) an approach to getting secondary outcomes into labeling.

6-21-01: This was a final preNDA meeting, focusing mostly on format issues for the NDA, but there was also discussion of drug abuse concerns. Lilly made the argument that atomoxetine is more like desipramine than a stimulant, and they backed this claim with preclinical and clinical data.

This NDA required reviews by the CMC, pharmacology/toxicology, biopharmaceutics, CSS, and clinical/statistical groups. The CMC review was conducted by Gurpreet Gill-Sangha, Ph.D. The pharmacology/toxicology review was conducted by Ikram Elayan, Ph.D. The biopharmaceutics review was conducted by Hong Zhao, Ph.D. The primary review of the efficacy data was done by Roberta Glass, M.D., from the clinical group, and Ning Li, Ph.D., from the Division of Biometrics. The primary review of safety data was done by Jerry Boehm, M.D. from the safety group.

The studies supporting this supplement were conducted under IND ~~_____~~ The original NDA was submitted 10-11-01, and a safety update was submitted 12-13-01.

We decided not to take this NDA to the Psychopharmacological Drugs Advisory Committee.

2.0 CHEMISTRY

I am not aware of any CMC concerns that would preclude an approvable action on this NDA. A number of deficiencies will be conveyed in the approvable letter, and the sponsor was alerted to these issues in a 7-15-02 telcon. The CMC group has found Lilly's proposed Description and How Supplied sections of labeling acceptable, however, they did bring to my attention a logo on the container label.

Lilly has proposed the name Strattera for this product, and DMETS has concluded that this name is acceptable.

3.0 PHARMACOLOGY

As of the date of completion of this memo, the pharmacology/toxicology review has not been finalized. However, I am not aware of any pharmacology/toxicology issues that would preclude an approvable action for this NDA.

4.0 BIOPHARMACEUTICS

The pharmacokinetics of atomoxetine have been adequately characterized and I am not aware of any biopharmaceutics concerns that would preclude an approvable action on this NDA.

The pharmacokinetics of atomoxetine can be summarized as follows:

- Atomoxetine has a Tmax at roughly 1-2 hours, and there is a modest food effect on Cmax, but not on AUC. With food, there is a 37% lower Cmax and a delay in Tmax by about 3 hours.
- Atomoxetine is cleared predominantly by 2D6, and therefore, 2D6 metabolizer status has a profound effect on clearance. PM's have a 10-fold greater exposure to atomoxetine than EM's.
- The major metabolite is 4-hydroxyatomoxetine that is equipotent to atomoxetine but present at much lower concentrations.
- The half-life of atomoxetine is about 5 hours in EM's and about 22 hours in PM's.
- Atomoxetine clearance is reduced by 50% in patients with moderate hepatic impairment and by 75% in patients with severe hepatic impairment.
- Weight-normalized atomoxetine clearance was roughly the same in normal subjects and patients with end stage renal disease.
- Atomoxetine does not appear to have much effect on the clearance of other drugs. However, atomoxetine clearance is greatly reduced by potent 2D6 inhibitors such as fluoxetine and paroxetine, with 6-8 fold increases in atomoxetine exposure.
- The major disagreement between OCPB and Lilly regarding labeling concerns 2D6 metabolizer status. Lilly proposed that no dose adjustment is needed in PM's, in patients with hepatic impairment, or in patients receiving concomitant fluoxetine or paroxetine; their argument seems to be that atomoxetine is adequately tolerated despite the much higher concentrations. OCPB recommends that clinicians consider using laboratory tests for genotyping patients, especially those who experience adverse effects. They also recommend dosing adjustments in patients with moderate to severe hepatic impairment (either 1/2 or 1/4 of the recommended starting dose, respectively) and in patients receiving concomitant fluoxetine or paroxetine (1/5 of the usually recommended dose). -Comment: I agree that these measures are needed (see later discussion under Safety).

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of efficacy was based on the results of 6 short-term, placebo-controlled trials (4 in pediatric patients with ADHD and 2 in adults with ADHD), and 1 long-term trial in pediatric patients with ADHD. In addition, efficacy data were collected in 4 open-label trials, however, these data are difficult to interpret and were not reviewed with regard to efficacy.

5.1.2 Summary of Studies Pertinent to Efficacy Claims

5.1.2.1 Study HFBD

This was a randomized, double-blind, parallel group, 9-week, flexible-dose study (7 US sites) comparing atomoxetine immediate release capsules (up to 2.0 mg/kg/day, given on a bid basis, i.e., before school and after school; the actual dose range was 10 to 90 mg/day), methylphenidate immediate release tablets (up to 1.5 mg/kg/day, given on a bid basis, i.e., before school and at lunch time), and placebo in children aged 7-12 meeting DSM-IV criteria for ADHD. This was an outpatient study. Randomization was stratified, based on prior methylphenidate exposure. Only patients naive to methylphenidate were randomized to this drug, and this was a small group, included only for assay sensitivity. The starting dose and dose increments were based on weight, and dose changes were based on efficacy and tolerability. The modified ITT samples for atomoxetine and placebo were 64 and 61, respectively. These represented combined samples for the methylphenidate naive and experienced patients. Overall, 73% of patients completed the study. The patients were about 4/5 male, about 83% Caucasian, and the mean age was 10 years. The mean final dose for atomoxetine was 1.6 mg/kg/day.

While the assessments included the ADHDRS-IV-Parent, the CTRS-R, the CPRS-R, and the CGI, all administered weekly, the primary outcome was change from baseline to endpoint in ADHDRS-IV-Parent total score, and I will comment specifically only on that outcome. This is an 18-item scale that maps directly to the 18 items that define ADHD in DSM-IV. Each item is rated from 0 (rarely/never) to 3 (very often). This scale was used by having investigators interview parents at each visit and then complete the scale. As is usually the case, the modified ITT data set included all randomized patients who received at least one dose of assigned treatment, and had baseline and at least one followup ADHDRS-IV-Parent assessment. The LOCF analysis was considered primary, but OC was also done. ANOVA was the statistical model employed. The overall analysis for ADHDRS-IV-Parent total score was highly significant ($p=0.0001$, for LOCF), and the OC analysis was also significant:

Efficacy Results on ADHDRS-IV-Parent Total Score for HFBD (LOCF)

	Mean Baseline ADHDRS	Mean Δ baseline ADHDRS	[P-value(vs pbo)]
Atomoxetine	41.2	-15.6	0.0001
Placebo	41.4	-5.5	

While not described here, results on various secondary endpoints also generally favored atomoxetine over placebo.

Comment: Both Drs. Glass and Li considered this a positive study, and I agree.

5.1.2.2 Study HFBK

This study was identical in design to HFBD, conducted at 10 US sites. The modified ITT samples for atomoxetine and placebo were 63 and 60, respectively. These represented combined samples for the methylphenidate naive and experienced patients. Overall, 79% of patients completed the study. The patients were about 4/5 male, about 80% Caucasian, and the mean age was 10 years. The mean final dose for atomoxetine was 1.5 mg/kg/day.

The overall analysis for ADHDRS-IV-Parent total score was highly significant ($p=0.0005$, for LOCF), and the OC analysis was also significant:

Efficacy Results on ADHDRS-IV-Parent Total Score for HFBK (LOCF)

	Mean Baseline ADHDRS	Mean Δ baseline ADHDRS	[P-value(vs pbo)]
Atomoxetine	37.8	-14.4	0.0005
Placebo	37.6	-5.9	

While not described here, results on various secondary endpoints also generally favored atomoxetine over placebo.

Comment: Both Drs. Glass and Li considered this a positive study, and I agree.

5.1.2.2 Study LYAC

This was a randomized, double-blind, parallel group, 8-week, fixed-dose study (13 US sites) comparing atomoxetine immediate release capsules in 3 fixed doses (0.5, 1.2, and 1.8 mg/kg/day, given on a bid basis, i.e., before school and after school), and placebo in pediatric patients aged 8-18 meeting DSM-IV criteria for ADHD. Randomization was 1:2:2:2 for these 4 groups, i.e., only half as many went to the low dose group as to the higher dose groups and placebo. This was an outpatient study. Randomization was stratified, based on 2D6 status (EM's vs PM's) and also prior methylphenidate exposure, for EM's. Patients in the higher dose groups were titrated to their target doses, with 5 days at each of the following steps: 0.8 mg/kg/day; 1.2 mg/kg/day. The modified ITT samples for atomoxetine groups and placebo were

as follows: low, 43; medium, 84; high, 82; placebo, 83. These represented combined samples for the methylphenidate naive and experienced patients, and for EM's and PM's. Percent completion ranged from 77 to 86%. The patients were about 70% male, about 75% Caucasian, and the mean age was 11 years. About 70% had prior stimulant exposure and 94% were EM's.

The primary outcome was change from baseline to endpoint in ADHDRS-IV-Parent total score, and I will comment specifically only on that outcome. The LOCF analysis was considered primary, but OC was also done. ANCOVA was the statistical model employed. The two primary comparisons were mid-dose vs placebo and high-dose vs placebo. These analyses were highly significant in favor of atomoxetine over placebo for LOCF ($p < 0.001$), and the OC analysis was also significant:

Efficacy Results on ADHDRS-IV-Parent Total Score for LYAC (LOCF)

	Mean Baseline ADHDRS	Mean Δ baseline ADHDRS	[P-value(vs pbo)]
Atmx 0.5	40.2	-9.9	0.155
Atmx 1.2	39.2	-13.6	<0.001
Atmx 1.8	39.7	-13.5	<0.001
Placebo	38.3	-5.8	

While not described here, results on various secondary endpoints also generally favored atomoxetine over placebo.

Comment: Both Drs. Glass and Li considered this a positive study, and I agree.

5.1.2.2 Study LYAT

This was a randomized, double-blind, parallel group, 6-week, flexible-dose study (9 US sites) comparing atomoxetine immediate release capsules (0.5 to 1.5 mg/kg/day, given on a qd basis, in the morning), and placebo in children aged 6-16 meeting DSM-IV criteria for ADHD. This was an outpatient study. Patients were started at 0.5 mg/kg/day for 3 days, then 0.75 mg/kg/day, and then increased to 1.0 mg/kg/day at the week 1 visit, if tolerated. Dosing was further increased to a maximum dose of 1.5 mg/kg/day if symptoms persisted. The modified ITT samples for atomoxetine and placebo were 84 and 83, respectively. Overall, 87% of patients completed the study. The patients were about 71% male, about 79% Caucasian, and the mean age was 10 years. The mean final dose in was 1.3 mg/kg/day.

The primary outcome was change from baseline to endpoint in ADHDRS-IV-Parent total score, and I will comment specifically only on that outcome. The protocol specified analysis was MMRM, but an LOCF analysis was also done. Both analyses very significantly favored atomoxetine over placebo, and I will provide the results only for the LOCF analysis.

Efficacy Results on ADHDRS-IV-Parent Total Score for LYAT (LOCF)

	Mean Baseline ADHDRS	Mean Δ baseline ADHDRS	[P-value(vs pbo)]
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Atomoxetine	37.5	-12.8	<0.001
Placebo	36.7	-5.0	

While not described here, results on various secondary endpoints also generally favored atomoxetine over placebo.

Comment: Both Drs. Glass and Li considered this a positive study, and I agree.

5.1.2.2 Study LYAA

This was a randomized, double-blind, parallel group, 10-week, flexible-dose study (14 US and 3 Canadian sites) comparing atomoxetine immediate release capsules (in a range of 60 to 120 mg/day, given on a bid basis, i.e., early morning and late afternoon/early evening) and placebo in adult outpatients (≥ 18) meeting DSM-IV criteria for ADHD. Randomization was stratified according to 2D6 metabolizer status (EM's vs PM's). Dosing was initiated at 60 mg/day, and increased as tolerated and needed for effectiveness to a maximum dose of 120 mg/day. The modified ITT samples for atomoxetine and placebo were 133 and 134, respectively. Overall, 75% of patients completed the study. The patients were about 64% male, about 88% Caucasian, and the mean age was 40 years. The mean final dose was 95 mg/day.

While the assessments included the Connors Adult ADHD Rating Scale-Investigator Rated: Screening Version (CAARS-INV:SV), the CGI, and the Stroop Color Word Test, all administered weekly, the primary outcome was change from baseline to endpoint in the 18-item ADHD symptom score from the CAARS-INV:SV, and I will comment specifically only on that outcome. This is an 18-item scale that maps directly to the 18 items that define ADHD in DSM-IV. Each item is rated from 0 (rarely/never) to 3 (very often). This scale was used by having investigators interview patients at each visit and then complete the scale. As is usually the case, the modified ITT data set included all randomized patients who received at least one dose of assigned treatment, and had baseline and at least one followup CAARS-INV:SV assessment. The protocol specified analysis was MMRM, but an LOCF analysis was also done. Both analyses very significantly favored atomoxetine over placebo, and I will provide the results only for the LOCF analysis:

Efficacy Results on ADHD Symptom Score for LYAA (LOCF)

	Mean Baseline ADHD-SS	Mean Δ baseline ADHD-SS	[P-value(vs pbo)]
Atomoxetine	33.6	-9.5	0.006
Placebo	33.2	-6.0	

While not described here, results on various secondary endpoints also generally favored atomoxetine over placebo.

Comment: Both Drs. Glass and Li considered this a positive study, and I agree.

5.1.2.2 Study LYAO

This study was identical in design to LYAA, conducted at 14 US sites. The modified ITT samples for atomoxetine and placebo were 124 and 124, respectively. Overall, 67% of patients completed the study. The patients were about 66% male, about 95% Caucasian, and the mean age was 42 years. The mean final dose was 95 mg/day.

Efficacy Results on ADHD Symptom Score for LYAO (LOCF)

	Mean Baseline ADHD-SS	Mean Δ baseline ADHD-SS	[P-value(vs pbo)]
Atomoxetine	34.9	-10.5	0.002
Placebo	34.2	-6.7	

While not described here, results on the OC analysis and various secondary endpoints also generally favored atomoxetine over placebo.

Comment: Both Drs. Glass and Li considered this a positive study, and I agree.

5.1.3 Comment on Other Important Clinical Issues Regarding Atomoxetine for ADHD

Evidence Bearing on the Question of Dose/Response for Efficacy

Only 1 of the 6 studies in this development, i.e., LYAC, provided data pertinent to dose response for efficacy. In that study, the lowest dose (0.5 mg/kg/day) was not effective, and there appeared to be no advantage for the highest dose (1.8 mg/kg/day) over the middle dose (1.2 mg/kg/day). For pediatric patients, the target dose should be 1.2 mg/kg/day, and the lack of demonstrated advantage of 1.8 over 1.2 mg/kg/day should be reflected in labeling. Labeling can reflect the fact that the safety of doses up to 1.8 mg/kg/day has been assessed and found to be adequate, however, I do not think that labeling should recommend pushing the dose up to this level in nonresponders, in the absence of data suggesting a benefit of such a practice. For adults, labeling will need to reflect the absence of knowledge for dose response for effectiveness, and will need to target the studied dose range of 80 to 120 mg/kg.

Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis of gender, age, and race. There was no indication of differences in response based on these variables, however, there was likely not adequate power to detect such differences.

Size of Treatment Effect

The effect size as measured by difference between drug and placebo in change from baseline in the ADHDRS observed in these studies was similar to that seen in other positive ADHD trials, and I consider this a sufficient effect to support an efficacy claim for this product in ADHD.

Duration of Treatment

As noted, a randomized withdrawal study was conducted for atomoxetine to examine longer-term efficacy. However, this study was clearly negative, and was not reviewed.

5.1.4 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence to support the claim of short-term efficacy for atomoxetine in pediatric and adult ADHD. The issue of longer-term efficacy will need to be addressed in the future.

5.2 Safety Data

5.2.1 Safety Database

Dr. Boehm's safety review of this NDA was based on an integrated database covering 31 trials in the ADHD program (17 clinical pharmacology studies and 14 phase 2-3 safety and efficacy trials). This included data from the original submission and also a 2-month safety update. In addition, some limited safety data were available from two earlier abandoned development programs

The ADHD program included 350 atomoxetine-exposed subjects in the clinical pharmacology trials and 2,337 atomoxetine-exposed subjects in the phase 2-3 trials (most of these were pediatric patients, with only n=270 adult patients). These ADHD atomoxetine exposures represent a total of 1,795 patient-years for the pediatric group and 205 patient-years for the adult group. For pediatric patients, there were 428 subjects exposed to a modal atomoxetine dose of at least 1.2 mg/kg/day for at least 6 months, and 129 such subjects for at least 1 year. A majority of subjects were male, i.e., 77% for the pediatric patients and 64% for the adult patients.

The findings from the two abandoned programs included data from 1,324 atomoxetine-exposed subjects. There were no postmarketing data since atomoxetine is not approved anywhere in the world.

5.2.2 Safety Findings and Issues of Particular Interest

5.2.2.1 Common and Drug-Related Adverse Events

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ON ORIGINAL

Common and drug-related adverse events included: anorexia; dizziness; nausea; vomiting; abdominal pain; constipation; weight loss; insomnia; sweating; and palpitations. Of note, for many of these symptoms, the incidence was higher for PM's compared to EM's in the database.

5.2.2.2 Vital Signs Changes (Blood Pressure and Heart Rate)

The vital signs data suggested slight increases in systolic and diastolic blood pressure and in heart rate in association with atomoxetine treatment. While there were several cases of syncope that were hard to interpret, there was also a suggestion of orthostatic hypotension with atomoxetine in short-term, placebo-controlled trials. These effects appeared to be somewhat greater for PM's compared to EM's, suggesting that these are dose related events. We are recommended that pulse rate and blood pressure be monitored periodically during treatment.

5.2.2.3 Growth Changes

There was a weight loss observed for atomoxetine vs placebo in the controlled trials, i.e., a mean difference of about 2 kg, and evaluation of uncontrolled longer-term pediatric longer-term data in comparison to predicted growth rates revealed lower than predicted increases in both weight and height. We are recommending that growth be monitored during atomoxetine treatment.

5.2.2.4 Urinary Bladder Outlet Symptoms

There was a signal for bladder outlet symptoms in the adult ADHD controlled trials database, with the following symptoms exceeding placebo for atomoxetine: urinary retention; urination impaired; dysuria; oliguria; and prostatic disorder.

5.2.2.5 Sexual Adverse Events

There was a signal for sexual side effects, and also menstrual symptoms, in the adult ADHD controlled trials database, with the following symptoms exceeding placebo for atomoxetine: impotence; abnormal ejaculation; orgasm abnormal; dysmenorrhea; and menstrual disorder.

5.2.2.6 Appendicitis

The appendicitis rate in the database was 2.5 times the background rate from Hospital Discharge Survey Data. There were no cases in the controlled trials, thus not permitting a controlled comparison within the NDA database. Dr. Boehm felt that it was not possible to draw any conclusions about causality for appendicitis, but recommended an expedited post-marketing followup for this event.

5.2.2.7 QTc Findings and Evaluations

The one possible clinical signal of a QTc effect came from a clinical pharmacology study (LYAE) in EM's and PM's, where the greatest increase oddly occurred at a predose timepoint for the highest dose group among the PM's, with a change from baseline of roughly 15 msec. There was no apparent QTc effect in the EM's in LYAE. In a second clinical pharmacology study (LYAY) utilizing artificially created PM's (by giving fluoxetine), this signal was not confirmed. However, as noted by the safety group, the atomoxetine exposures were not as high in this study as in LYAE. The phase 2-3 data did not reveal a QTc effect overall. However, again, a subgrouping of patients based on 2D6 metabolizer status suggested a greater proportion of QTc outliers for PM's compared to EM's. Preclinical data did reveal an IKR effect, thus possibly providing a mechanism for a QTc effect.

-On the basis of these findings, the safety group has proposed that 2D6 genotyping be a requirement of using atomoxetine to avoid exposing patients to a possible risk of QTc prolongation that may be clinically important. They have also recommended that labeling include a Warning statement regarding the potential for possibly clinically important QTc prolongation in PM's.

-Comment: I feel that this issue is unresolved, but in the absence of a satisfactory explanation for these admittedly limited findings, I agree that a conservative approach to labeling is appropriate, including the requirement to genotype patients prior to treatment. The problem, of course, is that noting this in labeling does not guarantee that genotyping will occur in practice. Consequently, it will be important to place the burden on Lilly to propose a risk management program for ensuring that genotyping is done and monitoring compliance with this requirement.

5.2.2.8 Abuse Potential

The sponsor has proposed labeling language stating that atomoxetine is not a controlled substance, is not a stimulant, and is not associated with diversion, rebound, or withdrawal.

-Since this drug is proposed for use in treating ADHD, and all of the drugs currently approved for ADHD can be classified as stimulants, we sought the advice of the Controlled Substances Staff (CSS) early in the planning stages for the NDA. In fact, we first asked for comment on the protocol for study LYAD in March, 2000. This was a single dose crossover "liking" study involving atomoxetine (ATM), methylphenidate (MPN), and placebo (PBO). CSS (in a 5-1-00 review) had no objections to the study design at that time, but rather, provided a general guidance document (that we transmitted to Lilly) and remarked that a program to assess abuse liability would need preclinical data as well as clinical.

-We first met with the sponsor to discuss their abuse liability program on 6-21-01, including CSS, and Lilly made the argument that neither animal nor human data thus far suggest that ATM has any abuse liability. CSS requested a complete briefing document, including relevant data from the sponsor, and this was provided on 7-13-01. They summarized their argument in favor of not scheduling ATM as follows:

-Both ATM and its major metabolite are specific NE reuptake inhibitors with little other activity; they are similar in this respect to the TCA desipramine. Drugs with this activity have not been associated with abuse potential.

-Animal studies did not suggest abuse potential.

-The one human abuse liability (LYAD) revealed a “non-liking” profile for ATM vs PBO, at the same time that MPH was shown to have a “liking” profile vs PBO.

-Finally, they indicated that the clinical trials with ATM revealed dose dependent dysphoric effects and no findings suggestive of diversion or abuse.

-In an 8-28-01 review of the 7-13-01 document, CSS concluded that not enough information had been provided for them to make a judgement about the abuse potential of ATM. They suggested that, based on what had been provided, there were findings of concern. In particular, they noted the generalization of ATM to cocaine in monkeys, and a relatively high affinity of ATM for GABA_A receptors and certain opioid receptors. They suggested that they could not interpret the summary findings provided for study LYAD and suggested that they may be interested in reviewing individual patient data rather than just group data.

-Lilly submitted another abuse liability package on 1-29-02, about 2 months after submission of the NDA. Their essential complaint was that they were not being given a clear approach by which they might demonstrate that ATM does not have abuse liability. We met with Lilly on 2-20-02, and there was some discussion of CSS’s earlier concerns about GABA_A and opioid activity, but given the extensive exploration of these potential activities by Lilly, CSS conceded that these were no longer of concern. However, CSS voiced continued concerns that there was generalization of ATM to cocaine in monkeys. Lilly disputed this conclusion, but nevertheless, had embarked on self administration studies in monkeys to finally address this concern, as requested earlier by CSS. However, CSS now indicated that such studies, even if negative, would no longer suffice, since they now had concerns about both the design and results of study LYAD. CSS argued that, at this point, only a better designed human abuse liability study would clear ATM of abuse liability. Lilly finally agreed to conduct an additional human study, and in fact, had already drafted a protocol for study LYBO, a study to be conducted in pure stimulant abusers.

-Based on comments from the 2-20-02 meeting, Lilly revised the protocol for LYBO and provided this in a 3-4-02 package. This was to be an 8-arm study, including 3 doses of ATM, 2 doses of MPH, 2 doses of desipramine (DSI), and PBO. CSS responded to this protocol in a 4-12-02 review, and these comments were provided to Lilly. Dr. Katz and I further discussed this protocol with Lilly in a 5-7-02 telcon. The basic approach in this study would be to proceed as follows: (1) first compare MPH and PBO, for validity of the assay; (2) next compare ATM and PBO; if equal, they would be done; (3) if ATM were liked vs PBO, then compare ATM with DSI; if equal, they would be done; (4) if ATM were liked vs DSI, then compare ATM with MPH. CSS advised adding phentermine in order to place ATM better on a continuum, in case ATM showed any liking properties. A major point of disagreement with the CSS comments on LYBO was their insistence that the ATM vs PBO test be a noninferiority test. This, of course, would require a much larger sample than is feasible in a study of this design, but it’s not clear this concern was ever resolved. A second point of disagreement throughout our discussions with CSS has been their insistence on the importance of examining individual data to look for patterns of difference in case group differences are not evident. Given the softness of the endpoints being looked at in these “liking studies,” this strikes me as a scientifically unsound approach, a view certainly shared by Lilly.

-As of this time, I am not aware of the progress of study LYBO, although undoubtedly it is not yet completed.

-We do have data from a safety review by Dr. Boehm suggesting no evidence of withdrawal symptoms in association with discontinuing atomoxetine. I am not aware of any evidence for abuse of atomoxetine in the clinical trials database, or of diversion.

-Comment: Based on the fairly extensive data already available, including the results from study LYAD, I see no findings even remotely suggestive of abuse potential. As of this time, we still do not have a review from CSS on the abuse liability package provided to them, nor do we have their recommendations regarding labeling. In the absence of such recommendations, I am inclined to leave the Drug Abuse and Dependence section as proposed by Lilly, with the understanding that further modifications may be needed when the CSS recommendations are forthcoming.

5.2.2.9 Allergic Adverse Events

Several adverse events often considered to represent allergic reactions and often considered to be possibly drug-related occurred in association with atomoxetine use, i.e., rash, urticaria, and angioedema. There is insufficient information to reach any conclusion about causality, nevertheless, the sponsor has proposed mentioning these events Warnings.

5.2.2.10 Mydriasis

There was a signal for mydriasis in the controlled trials database. We are recommending that atomoxetine not be used in patients with narrow angle glaucoma.

5.2.2.11 Once-Daily Dosing with Atomoxetine

The development program was conducted with twice daily dosing, with the exception of one trial with qd dosing. This regimen was effective and reasonably tolerated, and on this basis, the sponsor wants to include a recommendation for qd dosing at doses up to 1.8 mg/kg/day. However, it should be noted that this study only included dosing up to 1.5 mg/kg/day. The safety group has recommended that qd dosing be limited to 1.5 mg/kg/day, and that the differences in the common adverse event profile for qd vs bid dosing be included in labeling. I agree.

5.2.2.12 2D6 Metabolizer Status

A relatively small number of PM's were included in the development program, i.e., a total of 182, including 136 genotypic PM's and 46 phenotypic PM's (created by concomitant fluoxetine use). The safety group found no difference in SAE's or adverse dropouts between the EM's and PM's, however, they did find a number of other adverse events occurred more commonly among PM's than EM's (≥ 2 -fold). There was also a greater extent of pulse rate increase, weight loss, and reduction in height gain in PM's compared to EM's. The greater QTc effects in PM's have been described above.

-The safety group has recommended several modifications in labeling based on the PM/EM adverse event differences, including a section alerting prescribers to the observed differences in adverse events. As noted, they have also recommended that all patients be genotyped for 2D6 metabolizer status prior to treatment.
-Comment: I agree.

5.2.3 Conclusions Regarding Safety of Atomoxetine in ADHD

Overall, there were no safety findings that would preclude the approvability of this NDA.

5.3 Clinical Sections of Labeling

We have modified the clinical sections of the draft labeling that is included with the approvable letter. The explanations for the changes are provided in bracketed comments in the draft labeling.

6.0 WORLD LITERATURE

Dr. Glass reviewed the 8 literature reports provided by the sponsor. Apparently none of these reports for atomoxetine included any new serious adverse events that would impact on labeling.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, atomoxetine is not approved for any indication in any country at this time. We will ask for an update on the regulatory status of atomoxetine for the treatment of ADHD in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this NDA to the PDAC.

9.0 DSI INSPECTIONS

Inspections were conducted at 5 sites for atomoxetine studies; these sites represented all 6 of the efficacy studies supporting this NDA. It is my understanding that all 5 audits were considered to be acceptable with regard to using the data in support of this NDA.

10.0 LABELING AND APPROVABLE LETTER

10.1 Final Draft of Labeling Attached to Approvable Pa

Our proposed draft of labeling is attached to the approvable letter and the sponsor's draft labeling.

10.2 Foreign Labeling

Atomoxetine is not approved for the treatment of ADHD anyw

10.3 Approvable Letter

The approvable letter includes draft labeling and requests for a regulatory status update.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Lilly has submitted sufficient data to support the product as effective and acceptably safe in the treatment of ADHD. I am submitting an approvable letter with our labeling proposal and the above noted requests for final approval.

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cc:

Orig NDA 21-411

HFD-120

HFD-120.TLaughren/RKatz/JRacoosin/RGlass/JBoehm/AM

HFD-101/RTemple

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/s/

Thomas Laughren
7/31/02 09:48:14 AM
MEDICAL OFFICER

MEMORANDUM

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

DATE: July 16, 2002

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

VIA: Anna Marie Homonnay, Regulatory Project Manager
Division of Neuropharmacological Drug Products
HFD-120

Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Anne Trontell, M.D., M.P.H., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Patient Labeling for Strattera™ (atomoxetine),
NDA 21-411

The patient labeling which follows represents the revised risk communication materials for Strattera™ (atomoxetine) and has been reviewed by our office and by DDMAC. The revisions reflect changes in format, wording, and organization that are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. Comments are bolded, italicized, and underlined.

3 page(s) of
revised draft labeling
has been redacted
from this portion of
the review.

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

/s/

Jeanine Best
7/16/02 11:15:47 AM
CSO

Anne Trontell
7/23/02 03:58:34 PM
MEDICAL OFFICER

M E M O R A N D U M
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: July 31, 2002

To: Russell Katz, M.D., Director
Division of Neuropharmacologic Drug Products (HFD-120)

Through: Deborah B. Leiderman, M.D., Director
Controlled Substance Staff (HFD-009)

From: Katherine Bonson, Ph.D.
Michael Klein, Ph.D.
Ann-Kathryn Maust, M.D.
Controlled Substance Staff (HFD-009)

Subject: Abuse Liability Assessment of NDA 21-411
Strattera (atomoxetine hydrochloride)
Sponsor: Lilly

Background:

This consultation assesses the abuse potential and possible scheduling of atomoxetine under the Controlled Substances Act (CSA), as requested by the Division of Neuropharmacologic Drug Products (HFD-120). Atomoxetine is being developed for treatment of child, adolescent, and adult Attention-Deficit/ Hyperactivity Disorder (ADHD). All currently approved medications for the treatment of ADHD (methylphenidate, dextroamphetamine, and pemoline) are Schedule II or IV stimulants. The Sponsor proposes that atomoxetine not be controlled under the CSA, citing the results from nonclinical studies, clinical trials and a human abuse potential study (LYAD) as support for their position that atomoxetine lacks abuse potential and should be approved for marketing as a non-scheduled drug.

Conclusions and Recommendations:

Insufficient information was submitted by the Sponsor for full evaluation of the abuse liability of atomoxetine. Some preclinical data suggest that atomoxetine may have abuse liability. **Some clinical information exists on the abuse liability of atomoxetine, but additional clinical data are needed from studies that assess the abuse and dependence potential of atomoxetine in drug abusers who have histories of stimulant abuse. This includes results from Study LYBO, which is currently being conducted.** Specific recommendations regarding product labeling, the patient package insert and promotional material are included in this memorandum (Section III below).

I. Summary of Data Related to Abuse Liability from Preclinical Studies:

A. Biochemical Pharmacology

Atomoxetine was tested at a full range of neurotransmitter sites to assess binding affinity. There was relatively high affinity for only two sites in the brain: the norepinephrine (NE) transporter and the GABA-A receptor.

Atomoxetine (racemic as well as (+) and (-) isomers) has relatively high affinity for the norepinephrine transporter (NET). Atomoxetine inhibits the human NE transporter with a K_i value of 5.36 nM, as measured by an in vitro assay. The ability of atomoxetine to inhibit the NET produces a subsequent increase in NE levels in the prefrontal cortex. As would be expected of a drug that affects the NE system, some of the highest levels of atomoxetine in the brain following administration are found in the locus coeruleus.

There is less affinity of atomoxetine for the serotonin (5-HT) transporter ($K_i = 87$ nM). However, large increases in 5-HT levels in the prefrontal cortex and striatum were reported with higher systemic doses of atomoxetine. Atomoxetine has relatively poor affinity for the dopamine (DA) transporter ($K_i = 1451$ nM), as measured by an in vitro assay. Single doses of atomoxetine do not induce increases in DA levels in the striatum or nucleus accumbens, areas of the brain associated with reinforcement, but can increase DA levels in the prefrontal cortex.

Atomoxetine has moderate affinity ($K_i = 200$ nM) for the GABA-A receptor. However, electrophysiological assays with thalamic slices show that atomoxetine does not alter GABA-A-mediated inhibitory postsynaptic potentials (IPSPs), either positively or negatively. This suggests that a drug with relatively high affinity for the GABA-A site fails to show agonist, antagonist or positive modulatory properties functionally at this receptor. In the absence of behavioral data, it is not possible to conclude what functional activity atomoxetine has at the GABA-A site that might contribute towards its abuse.

The major metabolites of atomoxetine, desmethyl-atomoxetine and 4-hydroxy-atomoxetine, were assayed and found to have relatively high affinity for the NET and 5-HTT. 4-Hydroxy-atomoxetine has moderate affinity (101 nM) for the human mu opioid receptor. Functional assays at the mu opioid receptor show that 4-hydroxy-atomoxetine does not stimulate or inhibit GTPgammaS binding. It is not possible to conclude what functional activity atomoxetine has at the mu opioid site that might contribute to its abuse liability.

B. Behavioral Pharmacology

Overt behavioral responses to atomoxetine in animals are negligible at moderate doses but higher doses suppress spontaneous activity. Compared to the locomotor activity induced by methylphenidate and cocaine, atomoxetine does not affect locomotion. Extremely high doses produce convulsions and death in mice.

However, in drug discrimination studies, atomoxetine generalizes to cocaine in monkeys or rats trained to discriminate cocaine from saline. This suggests that atomoxetine has some properties similar to those of cocaine, but it is unclear whether these properties are related to reinforcement. Generalization of a drug to the cocaine cue often is predictive of abuse liability, but drugs that generalize to cocaine in animals include abusable drugs such as the stimulants amphetamine or methylphenidate, as well as drugs that are not recognized as abusable such as bupropion and imipramine.

Thus, in the absence of appropriately-designed human abuse liability studies, it is not possible to fully assess whether atomoxetine has reinforcing properties.

II. Summary of Data Related to Abuse Liability from Clinical Studies:

A. Clinical Trials Assessing Safety and Efficacy of Atomoxetine for ADHD

The Sponsor divided the Integrated Summary of Safety (ISS) into 8 analysis groups (3 primary and 5 secondary), and some patients were included in more than one analysis group. A limited number of case reports in the clinical trials suggest the possibility of isolated euphoric or stimulant-like responses to atomoxetine, but a clear signal indicative of abuse potential was not observed.

Below are comments on the three primary safety analyses.

1. Adult Acute Placebo-Controlled ADHD Analysis Group

The safety of atomoxetine in adult ADHD patients was evaluated by comparison of safety parameters between 270 atomoxetine-treated patients and 266 placebo-treated patients during an acute phase of up to 10 weeks in two double-blind studies (LYAA and LYAO). Atomoxetine doses ranged from 60 to 120 mg/day administered BID. The average modal dose was 99 mg/day.

Although the following findings were not statistically significant when atomoxetine and placebo patients were compared, only atomoxetine patients experienced the following events: euphoria (4 patients) and central nervous system stimulation (3 patients).

2. Child and Adolescent Acute Placebo-Controlled ADHD Analysis Group.

Safety parameters were compared between a group of 342 patients assigned to atomoxetine and a group of 208 patients assigned to placebo during treatment periods of 8 to 9 weeks in three double-blind studies. The majority of the atomoxetine patients received total daily doses between 1.2 and 2.0 mg/kg/day (administered BID). The average modal daily atomoxetine dose was 1.23 mg/kg/day.

One patient overdosed (described below) and another discontinued due to a medication-induced movement disorder that was diagnosed as tics and was of unclear significance. ADHD patients are more likely to develop tics than other patients, regardless of medication being taken.

Among unsolicited treatment-emergent adverse events, anorexia ($p = 0.002$) and weight loss ($p = 0.027$) occurred. One treatment-emergent adverse event was a withdrawal syndrome, but insufficient information was provided.

Using a solicited adverse event questionnaire (Barkley Behavior and Adverse Events Questionnaire-Modified [BBAEQ-M]), treatment-emergent decreased appetite ($p < 0.001$), drowsiness ($p = 0.029$), and dizziness ($p = 0.040$) were reported statistically significantly more often for atomoxetine-treated patients than for patients on placebo.

When compared to placebo, atomoxetine was associated with statistically significantly greater increases in mean changes in diastolic blood pressure and pulse and a greater decrease in mean change in weight. As per the Sponsor, none of these differences were thought to be clinically significant. Mean change in weight in the atomoxetine-treated group was -0.4 kg (-0.88 pounds). Mean change in weight in the placebo group was $+1.5$ kg ($+3.3$ pounds).

3. Child and Adolescent Overall ADHD Analysis Group.

Events reported in this Group and that may also predictably occur in individuals who take stimulants are "twitching/tics," "euphoria," "withdrawal syndrome," and "feeling unusually happy." However, a withdrawal syndrome may similarly occur in patients who discontinue desipramine. Hypomania, which is similar to euphoria and feeling unusually happy, may also occur in patients who are taking desipramine. Tics may occur in ADHD patients, regardless of the medication being taken.

The safety and tolerability of atomoxetine in ADHD patients was assessed by evaluating safety parameters in a group of 1,982 patients (6 to 18 years old) from multiple studies who were assigned to atomoxetine treatment BID. This database includes data from eight completed and ongoing child and adolescent ADHD studies of various lengths (acute and long-term) and designs (double-blind and open-label, controlled and uncontrolled). As there is no appropriate comparator group, this analysis deals with only atomoxetine patients and does not include placebo patients. Most patients in this group received atomoxetine at doses ranging from 1.2 to 2.0 mg/kg/day. The average modal daily dose was 1.3 mg/kg/day. Mean, median, and maximum lengths of atomoxetine therapy were 22 weeks, 15 weeks, and 118 weeks.

Adverse events included overdose, twitching, euphoria, and withdrawal syndrome. The two cases of overdose that occurred are described below.

Thirty-four of 1,933 patients (1.8%) were noted to have twitching, which is the COSTART term for tics. Four patients (0.2%) discontinued due to twitching and one

patient discontinued due to a movement disorder that was diagnosed as a tic disorder. For comparison, the most frequently reported events causing atomoxetine discontinuation were nervousness (8 patients or 0.4%) and somnolence (6 patients or 0.3%).

Seven of 1,933 patients experienced euphoria and one patient experienced a withdrawal syndrome. No additional information (e.g., patient numbers, histories) was provided for these patients.

Solicited events that were calculated from the Barkley Behavior and Adverse Event Questionnaire-Modified (BBAEQ-M), that may also be caused by stimulants, are "unusually happy" (180 patients or 11.8%), "talking too much" (246 patients or 23.8%), and "tics/motor movements" (117 patients or 7.6%). A placebo comparator was not part of this database.

The percentages of atomoxetine patients in the Child and Adolescent Acute Placebo-Controlled ADHD Analysis Group who reported "unusual happiness" and "tics/motor movements" on the BBAEQ-M were 6.3% and 5.2%, respectively. In this group the p values (comparing atomoxetine to placebo) for these items were 0.855 and 0.837, respectively. The percentages of patients in the Child and Adolescent Acute Placebo-Controlled ADHD Analysis Group who reported "talking too much" were 24.9% of the atomoxetine-treated patients and 28.1% of the placebo patients.

For comparison, the percentages of atomoxetine and methylphenidate patients in the Child and Adolescent Acute Methylphenidate-Controlled ADHD Analysis Group who reported "unusual happiness" and "tics/motor movements" on the BBAEQ-M are presented below (Table 1).

Table 1. Atomoxetine and Methylphenidate Patients Reporting "Unusual happiness" and "Tics/motor movements" on the Barkley Behavior and Adverse Event Questionnaire-Modified.

	Atomoxetine	Methylphenidate	Totals	p-value
Total Number	N=306	N=77	N=383	Fisher's
Item	n (%)	n (%)	n (%)	Exact
Unusually happy	35(11.8)	9(12.3)	44(11.9)	0.843
Tics/motor move	21(6.9)	4(5.2)	25(6.6)	0.797

In the Child and Adolescent Overall ADHD Analysis Group, changes in vital signs and weight were consistent with the changes noted for the Child and Adolescent Acute Placebo-Controlled ADHD Analysis Group, described above.

4. Withdrawal Effects.

The Sponsor's overall conclusion is that discontinuation of atomoxetine in children, adolescents, and adults is not associated with deleterious effects and that atomoxetine can

be stopped abruptly. In the combined and individual analyses of the two child and adolescent withdrawal studies, no statistically significant differences in AEs were observed between the atomoxetine and placebo groups during the withdrawal phase. In the individual analyses, similar statistically significant changes between the two groups were noted in weight and ECG HR.

In the combined analysis of the two adult studies, discontinuation-emergent dizziness occurred statistically significantly more often ($p = 0.035$) in the abrupt discontinuation group (5.5%) as compared to the taper group (0%). No other statistically significant differences were observed in the combined and individual analyses. Results of the combined analysis of the adult withdrawal studies suggest the need to taper atomoxetine prior to its discontinuation, in order to avoid dizziness.

5. Tolerance.

The Sponsor assessed whether tolerance occurs by evaluating changes in decreased appetite, weight loss, heart rate, and blood pressure. In healthy volunteers, tolerance to atomoxetine-related increased blood pressure was observed; tolerance to increased pulse was not observed.

In children and adolescents, the incidence of decreased appetite peaked during acute treatment, persisted for several weeks, and declined during long-term treatment. Also in children and adolescents, tachycardia tended to be reported as an adverse event more often early in treatment, and elevations of pulse and blood pressure tended to persist. Long-term data from the adult trials was not available when the tolerance section of the NDA was written.

6. Overdose.

Two child ADHD patients intentionally overdosed on atomoxetine. A 14 year old male intentionally took more medication than prescribed during a 3-week period. A 9 year old male intentionally ingested 15 capsules of study drug (10 atomoxetine and 5 placebo capsules).

7. Toxicity Due to Overdose.

According to the Sponsor, there were 7 cases of "modest" overdose in the child and adolescent ADHD trials. Of these 7 patients, 5 were inadvertently dispensed higher doses than specified by protocol. The other two are discussed above in Section 6. Overdose.

8. Diversion.

Three cases of diversion were reported by the Sponsor. There were two additional cases of suspected intent to sell or distribute atomoxetine.

9. Two Month Safety Update

In an analysis of 1,974 extensive metabolizer (EM) patients and 181 poor metabolizer (PM) patients, the following events were noted: euphoric mood (3 EM patients), overdose (2 EM patients), drug abuse (1 EM patient), and drug withdrawal syndrome (1 PM patient). Patient numbers or histories were not provided.

B. Clinical Abuse Liability Data

A clinical abuse liability investigation, study LYAD, compared the subjective responses of several doses of atomoxetine to the Schedule II stimulant methylphenidate and placebo in drug abusers.

The study is a randomized, double-blind, placebo and comparator-controlled, 6-arm treatment, 6-period, and crossover design. The six treatments are: placebo, three doses of atomoxetine (20 mg, 45 mg, and 90 mg) and two doses of methylphenidate (20 mg and 40 mg). Thirteen recreational drug users served as subjects, but there was no inclusion requirement for stimulant abuse or history of use. Measures of the behavioral effects are the study end-points which are assessed by evaluating treatment differences in the scores from the primary measure, the Visual Analog Scale (VAS), and two secondary measures, the Addiction Research Center Inventory (ARCI) short form and the Adjective Rating Scale (ARS). Eight endpoints are derived: VAS-Stimulated, VAS-Good, VAS-Like, VAS-Take Again, ARCI-Amp (amphetamine), ARCI-MBG (morphine/benzedrine group), ARS-Sedative and ARS-Stimulant. The Sponsor considered two responses: changes from baseline to average score and changes from baseline to the maximum post-baseline score.

The change from baseline (at 0 minutes) to 90 minutes after receiving the treatment appears to be the most relevant time for assessing behavioral effects than the average of responses over a period of four hours. The pharmacodynamic responses correlate with the peak plasma levels at 1-2 hours after oral administration, but do not correlate to the sum or average of all responses at all time points of the study.

As a known drug of abuse with a Schedule II designation, methylphenidate would be expected to significantly differentiate from placebo on subjective measures in order to validate the study design. There was a lack of statistically significant difference for methylphenidate at 20 and 40 mg from placebo on all but one primary endpoint (VAS-Good). On VAS-Stimulated and VAS-Like, only one dose of methylphenidate was significantly different from placebo (methylphenidate 40 and methylphenidate 20, respectively). Neither dose of methylphenidate was significantly different from placebo on the VAS-Take Again endpoint. This inconsistency in dose response for the positive control suggests potential study design problems and an inability of the study to successfully compare abuse liability of atomoxetine to that of methylphenidate.

On the secondary endpoints, the only measure where methylphenidate was different than placebo was on ARS-Stim, at a dose of 40 mg. For ARS-amp, ARS-MBG and even ARS-Sed, methylphenidate was not significantly different from placebo. Given the inability of methylphenidate to consistently differentiate from placebo, it is unclear how to interpret data from this study for atomoxetine.

In summation, there are a number of inadequacies in this study, which include: the doses of the positive control, methylphenidate, did not significantly differentiate on the subjective measures from placebo; volunteers were recreational drug users who were not required to have a history of stimulant abuse; there was wide variability in pre-drug baseline scores (0 to 50 on a 100-point VAS); and the study lacks statistical power because of a low subject number (n = 13).

C. Proposed Clinical Abuse Liability Study

The Sponsor has agreed to conduct study LYBO, a clinical abuse liability investigation that will compare the subjective responses of several doses of atomoxetine to the Schedule II stimulant methylphenidate, the Schedule IV stimulant phentermine, the unscheduled norepinephrine reuptake inhibitor desipramine, and placebo in stimulant-experienced drug abusers. Results from this study have not been submitted to FDA for evaluation and therefore are unavailable for inclusion in the present review.

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Draft Labeling

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revised draft labeling
has been redacted
from this portion of
the review.

**Attachment A:
CSS Review of Atomoxetine Pharmacology**

Study Summaries:

Biochemical Pharmacology Studies:

Study #05: Microdialysis studies of atomoxetine in rat brain

Atomoxetine administration (0.1, 0.3, 1.0, 3.0, 10.0 mg/kg, i.p.) produced a dose-dependent increase in norepinephrine (range of 225-340% of baseline) and dopamine (range of 160-400% of baseline) in the prefrontal cortex of rats that persisted for 4 hours, as measured by microdialysis. Serotonin levels decreased at 0.1 mg/kg (to 40% of baseline) and increased at 10 mg/kg (200% of baseline), but showed no change following intermediate doses.

A single dose of atomoxetine (10 mg/kg, i.p.) did not alter dopamine levels in the striatum but did increase serotonin levels to 300% of baseline for 4 hours. A single dose of atomoxetine (3 mg/kg, i.p.) did not alter dopamine levels in the nucleus accumbens, but did increase serotonin levels to 140% of baseline. Norepinephrine was not measured in the striatum or nucleus accumbens because of low levels and technical problems.

The Sponsor argues that the lack of an increase in dopamine levels in the striatum or nucleus accumbens indicates that atomoxetine does not have abuse potential. However, only single doses were used in this test. It is possible that repeated doses of atomoxetine may induce increases in dopamine in the striatum or nucleus accumbens.

Study # 07: Binding of atomoxetine and isomers at NE transporter

This biochemical study used synaptosomes from rat hypothalami to determine binding to the norepinephrine transporter, using racemic atomoxetine, as well as (-)atomoxetine and (+)atomoxetine.

<u>compound</u>	<u>Ki value for inhibition of [3H]norepinephrine uptake</u>
(-)atomoxetine	1.9 + 0.4 nM
(+)atomoxetine	16.8 + 4.5 nM
racemic atomoxetine	3.4 + 1.1 nM

These data demonstrate that all three compounds have high affinity for the norepinephrine transporter, but that rank order of affinity is: (-)atomoxetine > racemic atomoxetine > (+)atomoxetine.

Study #08: Acute effects of atomoxetine on central uptake of norepinephrine

One hour following administration of atomoxetine (1, 3, 10 mg/kg, i.p.),

(-)atomoxetine (1, 3, 10 mg/kg, i.p.), and (+)atomoxetine (5, 10, 20 mg/kg, i.p.) to rats, hypothalamic synaptosomes were assayed for inhibition of NE uptake. The ED₅₀ values were determined to be 3.4 mg/kg for atomoxetine, 6.3 mg/kg for (+)atomoxetine and 2.2 mg/kg for (-)atomoxetine. When blood levels of the isomers were plotted against the rate of NE uptake, the ED₅₀ in blood plasma was 110 ng/ml for (-)atomoxetine and 14 ng/ml for (+)atomoxetine. The (-) isomer was shown to have a duration of action of 2 hours, compared to that of the (+) isomer of less than 1 hour.

The isomers were also tested for their ability to protect against the 60% reduction in norepinephrine uptake produced by administration of the catecholamine neurotoxin, 6-hydroxy-dopamine. Pretreatment with the (-) isomer prior to 6-hydroxy-dopamine administration protected against neurotoxic effects in hypothalamic synaptosomes with an ED₅₀ of 4 mg/kg. Pretreatment with the (+) isomer prior to 6-hydroxy-dopamine administration protected against neurotoxic effects with an ED₅₀ of 22 mg/kg. These values may be higher than those in the study that did not use 6-hydroxy-dopamine because of competition for uptake with endogenous NE and the exogenous compounds.

Study #09: Affinities of atomoxetine, fluoxetine and other uptake inhibitors for NE uptake

Inhibition of [³H]atomoxetine binding to NE transporter site by various drugs

<u>Drug</u>	<u>pKi (M)</u>
desipramine	9.2
(-)atomoxetine	8.9
racemic atomoxetine	8.5
nomifensine	8.4
nortriptyline	8.3
(+)atomoxetine	8.2
imipramine	7.6
paroxetine	7.6
desmethyl-R-atomoxetine	7.6
desmethyl-atomoxetine	7.4
sertraline	7.3
fluoxetine	6.6
amphetamine	6.4

Study #10: Effect of atomoxetine and metabolites on monoamine uptake

Monoamine uptake inhibition in rat synaptosomes (K_i)

<u>Drug</u>	<u>5-HT</u>	<u>NE</u>	<u>DA</u>
atomoxetine	152 nM	4.5 nM	657 nM
para-hydroxy-atomoxetine	43 nM	3.0 nM	575 nM
desmethylatomoxetine	649 nM	92 nM	1430 nM
fluoxetine	29 nM	314 nM	--

Study #11: Binding of atomoxetine and cocaine to monoamine transporters

The affinity of atomoxetine and cocaine for the dopamine, norepinephrine and serotonin transporters (DAT, NET, 5-HTT, respectively) were assessed in clonal cells:

<u>Drug</u>	<u>DAT</u>	<u>NET</u>	<u>5-HTT</u>
atomoxetine	870 nM	36 nM	13 nM
cocaine	350 nM	1610 nM	260 nM

Thus, atomoxetine has higher affinity for the NET and 5-HTT than cocaine, but lower affinity than cocaine at the DAT.

Study #14: Autoradiography of binding sites for atomoxetine in rat brain

Autoradiograms generated with [3H]atomoxetine show that the highest levels of binding in the rat brain were in: bed nucleus of stria terminalis, thalamus, paraventricular nucleus of hypothalamus, locus coeruleus, nucleus of solitary tract, and inferior olive. Moderate binding was also seen in the median preoptic area, lateral and dorsomedial hypothalamus, superior colliculus, mammillary nuclei, zona reticulata of substantia nigra, ventral tegmental area, basolateral nucleus of amygdala and raphe nuclei.

Study #JS1: Inhibition of [3H]paroxetine and [3H]nisoxetine binding by atomoxetine

Atomoxetine was orally administered to rats at 2, 5, 10, 30, 60 mg/kg, p.o. Atomoxetine dose-dependently inhibited [3H]nisoxetine binding (representing binding at the norepinephrine transporter) with an ED50 of 2.4 mg/kg. However, at the highest dose of atomoxetine, there was only 30% inhibition of the serotonin transporter, as assayed with [3H]paroxetine. In time-course experiments, atomoxetine was shown to inhibit [3H]nisoxetine binding for up to 6 hours.

Study #PGT-2: Binding of atomoxetine and metabolites on NE, DA and 5-HT transporters

Binding assays were conducted with membranes expressing human and rat monoamine transporters, using [3H]nisoxetine for the NE transporter, [3H]mazindol for the DA transporter and [3H]paroxetine for the 5-HT transporter.

<u>Radioligand binding to membranes expressing human transporters (Ki)</u>			
	<u>5-HT</u>	<u>NE</u>	<u>DA</u>
Atomoxetine	87 nM	5.4 nM	1451 nM
Desmethyl-Atomoxetine	361 nM	780 nM	--
4-hydroxy- Atomoxetine	35.8 nM	25.2 nM	--
DesMe-4-hydroxy- Atomoxetine	--	976 nM	--

<u>Radioligand binding to rat transporters in frontal cortex or striatum (K_i)</u>			
	<u>5-HT</u>	<u>NE</u>	<u>DA</u>
Atomoxetine	133 nM	6.7 nM	2358 nM

These data show that, in membranes expressing human monoamine transporters, atomoxetine has very high affinity for the NE transporter, and relatively high affinity for the 5-HT transporter. Similar results were seen for the rat NE and 5-HT transporters. The 4-hydroxy metabolite of atomoxetine has high affinity for human NE and 5-HT transporters. There is relatively low, but still appreciable, binding of the desmethyl metabolite at human NE and 5-HT transporters.

Study #CNS329: Radioligand binding of atomoxetine and metabolites

Binding assays were conducted with atomoxetine and two metabolites on most major central neurotransmitter receptor systems in rat brain. There was negligible binding at all sites for atomoxetine and its metabolites with one exception. The para-hydroxy metabolite showed relatively high binding for three opioid receptors: mu opioid site (K_i = 422 nM), kappa-1 opioid site (K_i = 95 nM), delta opioid site (K_i = 300 nM). Although these K_i values do not qualify the para-hydroxy metabolite as an "opioid", administration of high doses of atomoxetine to humans may result in sufficiently high plasma levels of the para-hydroxy metabolite to produce significant opioid behavioral responses.

Study #PR9705: Receptor pharmacology studies of atomoxetine and metabolites

Additional binding assays were conducted with atomoxetine. The results show no significant binding at any of the major neurotransmitter sites with one exception. The K_i value for atomoxetine at GABA-A site was 200 nM. Although this does not represent very high binding at the GABA-A receptor, administration of high doses of atomoxetine to humans may result in sufficiently high plasma levels to produce significant GABA-associated behavioral responses.

Study #CNS 382:

Electrophysiological effects of atomoxetine HCl on GABA-A receptor activity in rat thalamic slices

Recordings were made from the ventrobasal nuclei of rat thalamic tissue slices to measure GABA-A receptor mediated neuronal activity. Electrical stimulation of reticular thalamic nuclei axons evokes monosynaptic, GABA-A receptor mediated inhibitory postsynaptic potentials (IPSPs) in ventrobasal neurons. These IPSPs are blockable with the GABA-A antagonist, bicuculline, or enhanced by the GABA-A receptor allosteric modulator, pentobarbital. Additionally, hyperpolarization of the resting membrane potential can be evoked with application of GABA or by the GABA-A agonist, muscimol. Glutamatergic responses in thalamic slices were blocked using an AMPA antagonist and an NMDA antagonist. GABA-B responses were blocked using a GABA-B antagonist.

The integrity of the assay was confirmed with GABA-A ligands. Bicuculline (0.1-10 μM) reduced the peak amplitude of IPSPs while pentobarbital (1-10 μM) increased the average area under the curve (AUC) of the evoked IPSP. Muscimol (1 μM) hyperpolarized the membrane potential and subsequent administration of bicuculline returned the membrane potential to control values.

Administration of atomoxetine at 10 μM did not change the average AUC of IPSPs. At 1 μM , atomoxetine did not affect the membrane potential of ventrobasal neurons and 10 μM did not reverse the hyperpolarization induced by 1 μM muscimol.

Similar experiments were conducted with nisoxetine, a norepinephrine reuptake inhibitor, with similar results. At 10 μM , nisoxetine did not change the AUC of IPSPs, nor did it alter the membrane potential of ventrobasal neurons.

Thus, neither atomoxetine nor nisoxetine have agonist, antagonist or positive modulatory activity at GABA-A receptors.

Study #CNS 381:

Pharmacological studies of atomoxetine using the human mu opioid receptor

The major metabolite of atomoxetine, 4-hydroxy-atomoxetine, has an affinity of 422 nM for the rat mu opioid receptor. In the present study, receptor binding in human mu opioid receptor was tested, and a functional assay of GTPgammaS binding was used to assess the activity of 4-hydroxy-atomoxetine at human mu opioid receptors. Agonists at the mu opioid receptor increase GTPgammaS binding, whereas antagonists at this receptor will block the increase in binding induced by an agonist.

Receptor binding assays showed K_i 's for human mu opioid receptor:

4-hydroxy-atomoxetine	101 nM
DAMGO	1.8 nM
morphine	0.9 nM
naltrexone	0.3 nM

Stimulation of GTPgammaS binding (as percent of maximum stimulation):

DAMGO	97%
morphine	63%
naltrexone	0.5%
4-hydroxy-atomoxetine	-1%

Inhibition of GTPgammaS binding by 4 μM DAMGO:

naltrexone (0.01 nM to 1.0 μM)	dose-dependent blockade
4-hydroxy-atomoxetine (0.01 nM to 1.0 μM)	no blockade

This suggests that despite a moderately high affinity for the mu opioid receptor, 4-hydroxy-atomoxetine acts as neither an agonist nor an antagonist in the GTPgammaS functional assay.

Preclinical Behavioral Pharmacology Studies:

Study #08: Drug discrimination between atomoxetine and cocaine in monkeys

Four monkeys were trained to discriminate 0.4 mg/kg cocaine. Three of the four monkeys identified atomoxetine as cocaine-like, although the dose that produced full generalization differed between monkeys. Doses of atomoxetine that generalized to cocaine were: 1.0 mg/kg, 10 mg/kg, and in one monkey 0.32 and 10 mg/kg (but not at 1.0 or 3.2 mg/kg). The fourth monkey did not respond on the cocaine lever at any dose of atomoxetine. The response rate of monkeys who identified atomoxetine as cocaine-like decreased as the dose of atomoxetine increased.

Study #09: Antagonism of cocaine discriminative cue by atomoxetine in rats

Atomoxetine was tested for its ability to antagonize the discriminative stimulus effects of 10 mg/kg cocaine in rats. No dose of atomoxetine tested (10, 25, 50 mg/kg) blocked the discriminative effects of cocaine.

Study #10: Drug discrimination between atomoxetine and cocaine in rats

Rats were trained to discriminate 10 mg/kg cocaine. Atomoxetine was tested at doses from 0.25-50.0 mg/kg for their ability to substitute for the cocaine cue. Partial substitution occurred between the doses of 2.5-50 mg/kg, with a maximum substitution of 77% at the highest dose. There were significant differences from vehicle control at 25 and 50 mg/kg. Two of six rats had seizures at 50 mg/kg. Response rate decreased with increasing dose of atomoxetine.

Study #12: Effect of intraperitoneal atomoxetine on behavior in mice

Mice were administered atomoxetine (10, 25, 50, 100 mg/kg, i.p.) and observed 20 minutes later for spontaneous behavioral responses. Locomotor activity was suppressed at 10 and 50 mg/kg. Other behaviors observed included shaking, rolling and turning. One of eight mice died within 50 minutes of receiving 100 mg/kg atomoxetine. The 60 minute duration of the observation period may have been too short to allow for the development of responses to atomoxetine metabolites, one of which has high affinity for opioid receptors.

Study #15: Effect of oral atomoxetine on behavior in mice

Mice were administered atomoxetine (25, 50, 100, 200, 400 mg/kg, p.o.) and observed 30 minutes later for spontaneous behavioral responses. No behavioral changes occurred at 25 mg/kg. At 50 and 100 mg/kg, mice exhibited decreased locomotion, slight weakness,

increased irritability, jerky gait, piloerection and tremors. At 400 mg/kg, clonic convulsions and death occurred. Maximum effects of all behavioral changes occurred at 20-30 minutes after administration of atomoxetine. Post-test feeding and weight was reduced following atomoxetine doses of 6.25-50 mg/kg. Atomoxetine (6.25-50 mg/kg) did not prevent the tonic extensor convulsions induced by pentylenetetrazole, but atomoxetine at 50 mg/kg did decrease convulsions induced by electroshock. There was no dose-dependent decrease in writhing induced by acetic acid. There was an increase in hexobarbital sleep time after doses of atomoxetine between 6.25-50 mg/kg.

Study #20: Effects of atomoxetine, methylphenidate and amphetamine on locomotor activity in mice

Atomoxetine (0.1-30 mg/kg, p.o.), methylphenidate (10-56 mg/kg, p.o.) and amphetamine (1-10 mg/kg, p.o.) were tested for their effects on locomotion in mice. There was a significant increase in locomotor activity following methylphenidate at 17.5-56 mg/kg and following amphetamine at 10 mg/kg. No increase in locomotion was seen following any dose of atomoxetine.

Study #PN9962: Acute behavioral effects of atomoxetine in rats

Rats received acute administration of atomoxetine (10, 50, 100 mg/kg, p.o.) and were observed for 6 hours. Female rats only showed a decrease in body temperature at 50 and 100 mg/kg. Lethargy was noted in male rats only at 50 and 100 mg/kg. There were no changes in behavior in auditory startle habituation, maze activity or passive avoidance learning.

Study #PN9984: Acute premonitory signs after atomoxetine in rats

Atomoxetine (100, 125, 150, 175, 200, 225, 250, 275, 300 mg/kg, p.o.) was administered acutely to rats and observed for 24 hours. One death occurred in a single female rat at 300 mg/kg, but no other deaths occurred in either sex at any dose. Overt signs of lethargy occurred at doses above 250 mg/kg, with occasional occurrences of myoclonic jerking. There was a transient increase in body temperature in male rats only at 300 mg/kg, while female rats showed a decrease in temperature at doses above 175 mg/kg. These doses are well above the equivalent human doses proposed for therapeutic use.

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Attachment A: Review of preclinical pharmacology studies

CC:

NDA # 21-411

HFD-009/ LeidermanD/ MoodyC/ BonsonK/ MaustAK/ AlpernD/ KleinM

HFD-120/ KatzR/ LaughrenT/ GlassR/ BoehmG/ Hommonay-Weikel AM

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/s/

Katherine Bonson
7/31/02 04:07:24 PM
PHARMACOLOGIST

Michael Klein
7/31/02 04:25:35 PM
CHEMIST

Signed for Deborah Leiderman, MD, Director, controlled Substance Staff

Meeting Minutes
Strattera™ (NDA 21-411)

Date: July 15, 2002

Time: 1.30 – 2.30 PM.

Type of Meeting: Conference Call

Attendees:

Food and Drug Administration

Division of Neuropharmacological Drug Products

Gurpreet Gill-Sangha – Chemistry Reviewer

Thomas Oliver – Chemistry Team Leader

Eli Lilly and Company

Mrs. Mary Barbara Miller – Regulatory Affairs, CMC

Dr. Sally Anliker – Manager, Regulatory Affairs, CMC

Dr. Kurt Lorenz – Drug Substance Process Scientist

Ms. Sue Bradley – Drug Product Formulation Scientist

Meeting Objective:

FDA initiated the conference call to get information on specific topics and to provide Lilly with current FDA thinking on some of the important deficiencies that would be addressed in the official FDA letter for N21-411. These deficiencies relate to the drug substance and drug product sections of N21-411. The following issues were discussed:

- FDA requested information on the commercial full scale batch sizes for the drug substance and drug product. Lilly stated that the batch size at the — facility for drug substance is the full scale commercial size. — facility has so far manufactured three batches from —. The Indiana site for drug substance manufactured batches at ¼ size ranging from — which were submitted to the NDA. The drug product information was provided as below:

Table 1.: Batch Sizes of Drug Product for Each Strength

Strength (mg)	Batch Size Manufactured (capsules)	Intended Commercial Size (capsules)
5	—	—
10, 25, 40	—	—
18	—	—
60	—	—

Based on the information for the drug product the 10, 18, 25, 40 and 60 mg strengths were manufactured at only 1/10th of the commercial size.

- FDA asked if the 18 and 60 mg strengths of drug product were manufactured at the Indiana site as reported in the drug product stability studies or was it a typographical

error. Lilly stated that the 18 and 60 mg strengths were manufactured at the Indiana site (CFN #1819470) and it was not submitted to the NDA as a drug product manufacturer. Lilly intended to provide Certificate of Analysis for the 18 and 60 mg strengths manufactured at the Puerto Rico site and show comparability to the Indiana site. However, no such data was submitted to the NDA.

- FDA voiced their concerns about the expiry date for the drug product based on the length and the quality of the data. Dr. Tom Oliver stressed that FDA was still reviewing the data and did not have a definite number for expiry date yet. Lilly wanted to know what sort of number the FDA was thinking about and Dr. Oliver said it would be a low number of about ~ months but the expiry date for the drug product was still under discussion. The expiry date for the drug product is under concern based on the quality of the data including lack of data from the drug product batches manufactured from the drug substance site in Ireland. In addition, the 18 and 60 mg strengths were not manufactured at the proposed commercial drug product manufacturing site in Puerto Rico, but at the non-commercial drug product manufacturing site in Indiana. Also, other variables including lack of information from Compound — a drug substance process impurity led to concern with the expiry date for the drug product.
- The re-test date for atomoxetine HCl was also voiced as a concern by FDA based on the lack of data from the commercial drug substance manufacturer in Ireland. No specific number for the re-test date was discussed.
- FDA also raised concern about the stability protocol for the drug product. It was noticed by FDA that the 30 count in 75 mL bottle was not on stability and this package appeared to be the most stressing stability condition relative to the 14 count in 50 mL and 60 count in 125 or 75 mL. Lilly would look into the protocol and make necessary changes for future.
- FDA also commented that the presentation of stability protocols for both the drug substance and drug product were unclear and confusing in their presentation and it would be helpful if the presentation had “x’s” across each time point for each test. Lilly appreciated the comment and would make improvements.
- Lilly was requested to respond to the detailed CMC questions in the official FDA letter as a response to the deficiencies.

FDA and Lilly thanked each other for their time and discussion.

Meeting Minutes Prepared by: Gurpreet Gill-Sangha, Ph.D. (chemistry Reviewer)
Concurred by: Thomas Oliver, Ph.D. (Chemistry Team Leader)

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/s/

Gurpreet Gill-Sangha
7/16/02 04:32:28 PM
CHEMIST

CMC Telecon

Thomas Oliver
7/16/02 04:37:57 PM
CHEMIST

MEMORANDUM

Date: August 8, 2002

From: John K. Leighton, Ph.D., DABT
Associate Director for Pharmacology/Toxicology, ODE I (acting for Dr. El Hage)

To: Dr. Robert Temple
Director, ODE I

Re: NDA 21-411
Strattera (atomoxetine, LY139603)

Background:

The Division has conducted a comprehensive review of the pharmacology and toxicology studies provided by the sponsor. In this review the Division has identified several deficiencies in the package that require phase IV commitments. These include:

- Additional *in vitro* genotoxicity studies (Ames and chromosomal aberration) are necessary to qualify impurity _____ as this impurity was not present in sufficient levels in studies conducted to date.
- A juvenile rat study with the impurity _____ spiked to a level of _____ should be conducted.

Other issues discussed in the pharmacology/toxicology review that are not fully addressed in recommendations by the Division include:

- The *in vivo* genetic toxicology study was considered inadequate for the metabolite nortomoxetine (compound 137877). No recommendation is provided by the Division for further study, or why additional studies are not necessary. Additional studies may not necessary be if this compound was assessed in the 2-year carcinogenicity studies.
- Based on preclinical findings (positive HERG assay, anesthetized dogs), the Division suggests careful monitoring of the ECG be conducted in the clinical setting. It's not clear how this recommendation is to be incorporated into practice.

Recommendations: The Division should reconsider the requirement for genetic toxicology for impurity compound _____. If this compound was positive in additional genotoxicity testing, carcinogenicity studies could be requested. This compound was present in sufficient levels in the mouse carcinogenicity study, which was negative. The review does not comment on the impurity level in the rat carcinogenicity study, but it should be noted that for at least parts of both studies the same lot (866-83F-249) was tested in both species. Therefore, it is not clear that additional genetic toxicity of this impurity would be of value.

I concur with the Division's justification and request for an additional study in juvenile animals.



The Division should address whether additional genetic toxicology testing is necessary for compound 137877.

The Division should clarify recommendations to monitor ECG.

Additional comment:

- The label should clearly explain the terms EM and PM that are discussed in the carcinogenicity section.
- Milk excretion data should be incorporated into the label.

Dr. Rosloff provides the following comments in response to my recommendations, and I concur with his comments.

1. Regarding genotox testing of the impurity, we have discussed the issue internally again and have decided to still ask for the studies. We had thought extensively about this in the past. Our thinking is that even though the impurity was adequately tested in the mouse CA study, if it were shown to be genotoxic, we would want a rat CA study to more definitively determine carcinogenic potential. If it were carcinogenic, it would likely lead to further action, e.g. requiring removal of the impurity or possibly even removing the drug from the market. (You also note that the same drug lot was used in both the rat and mouse carcinogenicity studies "for at least parts of both studies"; however the only lots used in the rat study had inadequate levels of the impurity [the mouse study did use one of these inadequate lots but only for a short period of time during the study]).

2. Additional genotox testing is not necessary for this metabolite. No testing was required in the first place. It is present in all species.

3. We are requesting additional human QT info which may be added to labeling pending outcome.

4. The terms EM and PM are not used in the Carcinogenicity section.

5. Rat milk excretion is mentioned in the Nursing section.

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/s/

John Leighton
8/9/02 11:03:15 AM
PHARMACOLOGIST

Executive CAC

Date of Meeting - May 14, 2002

Committee: Joseph Contrera, Ph.D., HFD-901, Acting Chair
Abigail Jacobs, Ph.D., HFD-540, Alternate Member
Al DeFelice, Ph.D., HFD-110, Alternate Member
Barry Rosloff, Ph.D., HFD 120, Team Leader
Ikram M. Elayan, Ph.D., HFD 120, Presenting Reviewer

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The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA # 21,411

Drug Name: atomoxetine hydrochloride

Sponsor: Eli Lilly

Background: atomoxetine hydrochloride is a norepinephrine reuptake inhibitor intended for the treatment of ADHD in both children and adults. The compound was not genotoxic in Ames test, in *in vitro* chromosomal aberrations in CHO cells, and in *in vivo* micronucleus in ICR mice.

Rat Carcinogenicity Study: two replicate studies each with 30 rats/sex/group were conducted two weeks apart. Tomoxetine at concentrations of 0.0, 0.01, 0.03, and 0.1% was administered orally in diet for two years. These levels were kept constant and were not adjusted for changes in body wt. These levels represented time-weighted average daily doses of 4&5 mg/kg at LD, 13&15 mg/kg at MD, and 43&51 mg/kg at HD in M and F, respectively. Doses used in this study were based on findings from previous 3-month and 1-year toxicity studies at concentrations up to 0.1% in which decreases in body weight of 10-17% compared to control were reported. The results of this study indicated a decrease in body weight in M at HD (5% compared to control) and F at HD (15%), MD (7%) and LD (3%) at the end of the study. Moderate (M and F) to severe (M) progressive glomerulonephrosis was observed with treatment. In light of these findings, an MTD was considered to have been reached. A decrease in food consumption was seen with treatment in both M and F. This decrease was also seen in studies where the drug was administered by gavage suggesting that the decrease in food consumption was an effect of the drug rather than due to poor palatability. There was no obvious tumor development in response to treatment.

Mouse Carcinogenicity Study: two replicate studies each with 30 mice/sex/group were conducted two weeks apart. Drug was administered orally in diet at fixed concentrations of 0.0, 0.03, 0.1, and 0.3%. Doses were estimated (from body weights of animals on the study and food consumption of the historical control) to be 34 mg/kg at the LD, 120&124

mg/kg at the MD, and (corrected for the decrease in food consumption observed in a later study) 401&422 mg/kg at HD in M and F, respectively. Doses used in this study were based on doses used in a 3-month toxicity study (0.025, 0.1, and 0.4% tomoxtine was given orally in diet) where decreases in body wt of 13% compared to control in M and 9% in F were reported. In the carcinogenicity study death occurred earlier in M at the HD in comparison to the control group. Decreases in body wt at MD (7% compared to control) and HD (19%) in M and MD (10%) and HD (32%) in F were reported at the end of the study. Based on these findings an MTD is considered to have been reached. There was no obvious tumor development in response to treatment.

Executive CAC Recommendations and Conclusions:

The committee concurred that the rat study was adequate and an MTD was reached based on the decrease in body weight, which was considered a drug effect since this decrease was also observed in gavage studies. The committee also concurred that there were no significant tumor findings in response to treatment.

An MTD was also considered to have been reached in the mouse study based on the increase in mortality rate in male mice at the high dose and the decrease in body weight. The committee concurred that the study was adequate and that no significant tumor findings were observed in response to treatment.

Joseph Contrera, Ph.D.
Acting Chair, Executive CAC

cc:\n
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