CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-411

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

IND —

Lilly Research Laboratories
Attention: Rex Souter, Ph.D.
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Souter:

Please refer to the Written Request, originally issued on October 10, 2001, that you received from the Center for Drug Evaluation and Research. This Written Request was issued under Section 505A of the Federal Food, Drug, and Cosmetic Act to conduct pediatric studies using atomoxetine hydrochloride. As you know, on January 4, 2002, the President signed into law the "Best Pharmaceuticals for Children Act," (BPCA) which both extended the pediatric exclusivity program established in the 1997 FDA Modernization Act (FDAMA) and provided new mechanisms for studying pediatric uses for drugs. The BPCA also contains new provisions of which you should be aware related to user fees, priority review, drug labeling, and disclosure of pediatric study results. FDA is revising its Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act to provide additional information on the pediatric drugs study provisions of the BPCA.

FDA has received questions about whether sponsors who were issued Written Requests to conduct pediatric studies prior to passage of the BPCA, but who had not as yet submitted the reports of the studies as of January 4, 2002, would be governed by the provisions of FDAMA or the BPCA. In order to maximize the benefit to be derived from the BPCA and to minimize uncertainty and delay in implementing the pediatric exclusivity program, FDA has decided to reissue those Written Requests originally issued prior to passage of the BPCA for which studies have not already been submitted.

This letter is your notification that the Written Request (and any subsequent amendments) described above is considered to be reissued as of the date of this letter. The terms of the Written Request are not otherwise altered by this letter. If you believe that the Written Request should be amended, please contact the division directly.

Please note that if the original Written Request was issued under Section 505A(a), it will now be considered to be issued under Section 505A(b), due to the reordering of the sections, as described in Section 19 of the BPCA. If the original Written Request was issued under Section 505A(c), it will still be considered to be issued under Section 505A(c).

An important change to note is that, if the drug for which FDA issued the Written Request under 505A(c) has listed patent or exclusivity protection, new section 505(d)(4)(A) states that within 180 days of receipt of this "reissued" Written Request, you must notify FDA when the pediatric studies will be initiated, or that you do not agree to conduct the requested studies. New provisions at Section 505(d)(4)(B)-(F) describe alternative methods for obtaining these pediatric studies.

If you have questions regarding the BPCA, please contact the Division of Pediatric Drug Development at (301) 594-7337. As noted above, requests to amend your Written Request should be directed to the review division.

Sincerely,

{See appended electronic signature page}

M. Dianne Murphy, M.D.
Director
Office of Counter-terrorism and Pediatric Drug Development
Center for Drug Evaluation and Research

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/s/

Dianne Murphy
7/2/02 06:21:45 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-411

Eli Lilly and Company
Attention: Gregory Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, Indiana 46285

Dear Dr. Brophy:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: [redacted] (atomoxetine hydrochloride) capsules

Review Priority Classification: To Be Determined

Date of Application: October 11, 2001

Date of Receipt: October 12, 2001

Our Reference Number: NDA 21-411

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on December 12, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be August 12, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug
Products, HFD-120
Attention: Division Document Room 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug
Products, HFD-120
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you should have any questions, please call Ms. Anna Marie Homonnay, R.Ph., Regulatory Health Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Anna-Marie Homonnay
10/18/01 01:24:44 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND —

Lilly Research Laboratories
Attention: Rex Souter, Ph.D.
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Souter:

Reference is made to your Proposed Pediatric Study Request submitted on June 12, 2000, (N-152) for Atomoxetine Hydrochloride to IND —

To obtain needed pediatric information on atomoxetine hydrochloride, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies:

General Advice for Developing a Drug for ADHD in the Pediatric Population

Attention deficit hyperactivity disorder (ADHD) has been recognized as a common childhood disorder. Although there is recent recognition of ADHD as possibly a disease of adulthood as well, drug development for this indication has focused on the pediatric population where treatment of this disorder is most prevalent and widely recognized. It is also noted that the literature heavily emphasizes the disease as existing in children and adolescence. According to DSM-IV criteria, symptoms of ADHD must be present before age 7. Because the target population for drug development for the treatment of ADHD is primarily the pediatric population, and it is not well established that adult ADHD is simply an extension of pediatric ADHD, it is not appropriate to extrapolate effectiveness based on adult data. For these reasons, it is felt that confirmation of efficacy of a new molecular entity for the treatment of ADHD would require two placebo-controlled studies conducted in the pediatric population. In addition, an ADHD program in the pediatric population would need to include pharmacokinetic information and safety information in the relevant pediatric age groups. For ADHD in the pediatric population, we consider the relevant age groups to include children (ages 6 through 11) and adolescents (ages 12 through 17). At this point in time, we are not including the preschool population, even though there is now fairly wide agreement that ADHD is a recognizable entity in this younger population. One difficulty is a lack of validated diagnostic and assessment methods for this younger population. In general, the methodology for conducting studies in the preschool age group has not been well-established, and this would serve as a barrier to the conduct of such trials.

- *Types of studies:*

  Pediatric Efficacy and Safety Studies

  Pediatric Pharmacokinetic Study

  Pediatric Safety Study

- *Indications to be studied (i.e., objective of each study):* The overall goal of the development program is to establish the safety and efficacy of the study drug in the treatment of ADHD in the pediatric population, and to develop other information, e.g., pharmacokinetic, pertinent to using the drug in the pediatric population.

Study Design

Pediatric Efficacy and Safety Studies

For the controlled efficacy studies, you must conduct two randomized, double-blind, placebo-controlled acute treatment trials, with a recommended duration of at least 3 to 4 weeks. We recommend that at least one of the two studies should be a fixed dose study including two or more fixed doses of the study drug. You may consider dosing patients on the basis of patient weight. Ideally, a relapse prevention trial would follow from the acute treatment trials, involving the randomization of responders from the acute treatment trials to continuation on either study drug or placebo, with follow-up observation for relapse for a period of 6 months or more.

Pediatric Pharmacokinetic Study

You must obtain pharmacokinetic data to provide information pertinent to dosing of the study drug in the relevant pediatric population. These data could come from traditional pharmacokinetic studies, or alternatively, from population kinetic approaches applied to controlled efficacy trials or to other safety trials. You should be aware that a guidance document on population pharmacokinetic studies is available under [www.fda.gov/cder/guidance/1852fnl.pdf].

- *Age group in which study(ies) will be performed:*
- *Study endpoints*
- *Drug information*
- *dosage form:*
- *route of administration:*
- *regimen:*
- *Drug specific safety concerns:*
- *Statistical information, including power of study and statistical assessments:*
- *Labeling that may result from the study(ies):* Appropriate sections of the label may be changed to incorporate the findings of the studies.
- *Format of reports to be submitted:* full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. INCLUDE OTHER INFORMATION AS APPROPRIATE
- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before INSERT DATE. Please remember that pediatric exclusivity extends only existing patent protection or exclusivity that has not expired or been previously extended at the time you submit your reports of studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as **a new drug application or as a supplement to an approved NDA** with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the

beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you should have any questions, please call Ms. Anna Marie Homonnay, R.Ph., Regulatory Health Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Homonnay Weikel, Anna M

From: Moody, Corinne P
Sent: Tuesday, April 09, 2002 2:07 PM
To: Homonnay Weikel, Anna M
Cc: Locklear, Dannette M; Moody, Corinne P
Subject: Atomoxetine minutes and handouts

Hi Anna Marie,

I tried to send this to you earlier, but i had so much in my inb0x, i had to delete some things before I could actually send any messages.

Attached you will find our revisions to the FDA atomoxetine minutes. We are sending a version with the revisions and deletions visible in color, as well as a cleaned up copy with only the corrected text for ease of reading.

We decided not to revise the Lilly minutes line by line, but we do have a few comments:

1) Lilly suggests that incidents of overdose and diversion in the clinical trials are of little consequence. However, as noted in our presentation at the meeting with Lilly (see our attachment), incidents of overdose and diversion are part of a full abuse liability assessment.

2) CSS routinely analyzes both group and individual patient results in clinical abuse liability study LYAD because there were wide standard deviations and a lack of statistical power.

3) CSS recommended inclusion of a Schedule IV stimulant, such as phentermine. Desipramine was also discussed as a possible comparator.

4) Lilly's assertion is incorrect that "FDA agreed that if the LYBO results do not suggest abuse potential based on the analysis plan to be presented, then atomoxetine would be labeled as an unscheduled drug." FDA will take all data into consideration when making labelling and any scheduling recommendation. We do not make a priori agreements with companies before review of all data.

When you send out the final minutes, would you please attach all documents provided to Lilly by CSS during the meeting? We are attaching these documents electronically for your convenience.

Let us know if there's anything else we can do.

Thanks --

Ann-Kathryn, Kit, Mike, Corinne, Deborah


atomMINchanges.doc


atomMINclean.doc


atomoverhead.doc


CLINslides.doc


revised LYBO protocol.doc


CSS quest.doc

Clinical Trial Data

The following are incidents of concern, and we requested additional information regarding these incidents yesterday.

1. **Intentional Overdose**

   One ADHD patient (Pt. HFBF-004-1125) intentionally took more atomoxetine than prescribed.

   One patient in the MDD trials "possibly" overdosed on "study drug" for an unknown reason. This overdose was described as intentional.

2. **Drug Diversion**

   Three drug diversion incidents that were reported during the ADHD trials are of concern and require further explanation.

Comments on Study LYAD

1. There were 16 subjects and 14 completers.

2. The study was done on an outpatient basis. It is better to conduct abuse liability studies on an inpatient unit because of the nature of the subject population.

3. The population had a heterogeneous drug use status. Subjects were "recreational drug users" who did not meet criteria for drug dependence and did not have a history of substance abuse disorder. Thus, it is not clear that subjects who had used stimulants actually liked stimulants, and some of them may have tried stimulants only once. The subjects should have liked stimulants and should have had a history of recent stimulant use.

4. Use of a single comparator may be a limitation of this study. For example, it would have enhanced the study to compare atomoxetine to a Schedule II and a Schedule IV substance, such as phentermine.

5. Some AEs that occurred in Study LYAD, such as anorexia, anxiety, euphoria, and "unexpected benefit," appear to be consistent with stimulant effects.

6. A statistical consult is pending because of the wide standard deviations observed. Because the study was small and the population was heterogeneous, it is important for the individual subject data to be reviewed.

2/19/02

Atomoxetine—CSS Questions for Sponsor Regarding Study LYAD and Data from the Clinical Trials

1. Please clarify the AE Subject Data Listings that appear on pages 348-389 of the LYAD Study Report and in the electronic datasets. These listings appear to have been miscoded. For example, according to page 348, S6001 experienced anorexia, anxiety, chills, and confusion after taking MPH 20 (methylphenidate 20 mg). However, the visit period during which these events occurred is listed as "50." According to the definitions of visit time periods on page 253 of the study report, period 50 would be the period after S6001 received ATX 90 (atomoxetine 90 mg) and before S6001 received MPH 20. (MPH 20 was administered during period 52, as per the definitions on page 253.) Please provide another list of AEs in which the AEs are listed next to the name of the last drug that was administered before they occurred. For all subjects, please provide the AEs, dates on which they occurred, time period during which they occurred, and the name of the last drug received before they occurred. Please also provide details from the original records and/or the investigator's narrative regarding the AEs that S6001 experienced during periods 50 and 70.

2. Some AE data listings appear to be missing in the LYAD study report and the electronic datasets for the following subjects: 6001, 6005, 6013, 6016, and 6020. Please provide all the AE data for these subjects, even if the AE data for a specific time period is recorded as "none."

3. Please provide the investigator's narrative (and information from the original records if the narrative does not explain or describe AEs sufficiently) for the following study LYAD subjects: 6009, 6015, and 6018. S6009 experienced euphoria after taking ATX 20 and 45 and MPH 20 and 40. S6015 and S6018 experienced an "unexpected benefit" after taking ATX 20 (during periods 42 and 50, according to the time period definitions on p. 253 of the study report) and ATX 45, respectively.

4. Please clarify the adverse event information on page 119 of the LYAD study report. Above the table, the sponsor states that the table was developed using the second definition of treatment-emergent events. (See paragraph at top of p.119 for the first and second definitions, or descriptions of the first and second analyses.) However, below the table, the sponsor seems to state that the table was developed by using the first definition or first analysis. If the table was developed by using the second definition, the table appears to be inconsistent with S6001's data listing. S6001 developed "anorexia, anxiety, chills, confusion" after taking ATX 90 (see above), but only chills are listed as an adverse effect due to ATX 90 in the table on page 119. In addition, as per the data listings and the time period definitions on p. 253, both S6009 and S6012 experienced vomiting on the days they received ATX 90. However, as per the table on p. 119, only one subject had vomiting after receiving ATX 90. Finally, the table does not include all types of adverse events noted in the Subject Data Listings section of the study report.

It is unclear how meaningful the table is if it was developed using the first analysis. Valuable information regarding AEs may not be included if only AEs that occur in the office (and not any time after a dose of study drug is administered and before the next dose is administered) are presented in the table.

Please explain the table or provide a revised table.

5. One ADHD patient (Pt. HFBF-004-1125) intentionally took a greater atomoxetine dose than the one prescribed. The sponsor states that this case does not appear to be an attempt to abuse atomoxetine but does not state why. Please provide the investigator's narrative (and information from the original records if necessary) to explain the case.

6. Please provide more information regarding the drug diversion incidents that occurred in the following patients: LYAB-021-4698, LYAB-048-4968, and LYBB-037-665. Please provide the investigator narratives (and details from the original records if necessary) to explain these cases. Examples of questions that should be answered follow. Why did the patients try to sell/distribute their atomoxetine? Was it because of the effects they experienced when they took it? Did they ever take more than the prescribed dose? If so, how did they feel? Why did one patient's friend (who has a history of drug abuse) steal the patient's atomoxetine? Did the patient tell the friend that atomoxetine made the patient feel good?

7. During the clinical trials of 1275 adults with MDD, one patient "possibly" overdosed on "study drug" (?atomoxetine) for an unknown reason (second patient listed on p. 24 of the July 2001 Abuse Potential Briefing Document.) The overdose was described as intentional and was not clearly labeled as a suicide attempt. Please explain the case by providing the investigator's narrative (and details from the original records if necessary).

8. Please describe the exact methodology used to search the data from the adult MDD trials for events related to drug abuse or diversion. Were the search terms used only the ones listed on p. 24 of volume 1 of the July 2001 Abuse Potential Briefing Document? Was all the data searched (not just the serious adverse event listings) by using the following terms: drug abuse/dependence, misuse, diversion, overdose, withdrawal, addiction, discontinuation syndrome/symptoms? Was a similar search done of the ADHD trial data?

9. Please provide as soon as possible the CRFs for all 16 subjects who received study drug during study LYAD.

In vitro binding to monoamine reuptake sites in brain

Compound	Ki (nM) [^{3}H] NET	[^{3}H] 5-HTT	[^{3}H] DAT
RAT:			
Atomoxetine	**5**	**152**	**657**
4-OH-Atomoxetine	**3**	**43**	**575**
Desmethylatomoxetine	**92**	**649**	**1430**
HUMAN:			
Atomoxetine	**5.4**	**87**	**145**
4-OH-Atomoxetine	**25.2**	**35.8**	--
Desmethyl-Atomoxetine	**780**	**361**	--

Schedule II stimulants (methylphenidate, methamphetamine, amphetamine, cocaine) show Ki's of:

45 - 175nM for NET
580 - 14,900 nM for 5-HTT
115 - 300 nM for DAT

Schedule IV stimulant (phentermine) shows Ki's of:

180 nM for NET
11,170 for 5-HTT
580 nM for DAT

Unscheduled monoamine uptake inhibitors (nomifensine, bupropion, fluoxetine, venlafaxine, desipramine, imipramine) show Ki's of:

2 - 2590 nM for NET
10 - 18,310 nM for 5-HTT
90 - 6900 nM for DAT

* Atomoxetine, major metabolites had binding Ki's of > 1000 nM at most major central neurotransmitter receptor systems in rat brain, except for:

Atomoxetine	GABA-A	200 nM
4-OH-atomoxetine	mu opioid	422 nM

* Further testing of GABA-A effects from atomoxetine:

Recording in ventrobasal nuclei of rat thalamic tissue slices to measure GABA-A receptor mediated inhibitory postsynaptic potentials (IPSPs).

Pentobarbital (GABA agonist), 1-10 uM -- increased average AUC of IPSPs
Bicuculline (GABA antagonist), 0.1-10 uM -- reduced peak amplitude of IPSPs
Muscimol (GABA agonist), 1 uM -- hyperpolarized the membrane potential,
blockable with bicuculline

Atomoxetine, 1 uM -- no affect on the membrane potential
10 uM -- no change in average AUC of IPSPs,
no reversal of hyperpolarization induced by muscimol

Thus, atomoxetine does not have agonist, antagonist or positive modulatory activity at GABA-A receptors.

* Further testing of opioid effects from 4-hydroxyatomoxetine:

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

4-OH-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-OH-atomoxetine	-1%

Inhibition of GTPgammaS binding by 4 uM DAMGO:

naltrexone (0.01 nM to 1.0 uM) dose-dependent blockade

4-OH-atomoxetine (0.01 nM to 1.0 uM) no blockade

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

* Microdialysis in rat brain following atomoxetine (0.1, 0.3, 1.0, 3.0, 10.0 mg/kg, i.p.) showed:

  increase in NE, DA in prefrontal cortex (no change in 5-HT)

  increase in 5-HT in striatum (no change in DA, NE)

  increase in 5-HT in nucleus accumbens (no change in DA, NE)

* Atomoxetine (6.25-50 mg/kg) reduced post-test feeding and weight in mice.

* Atomoxetine (0.1-30 mg/kg, p.o.) did not induce any increase in locomotion in mice, although there was a significant increase in locomotor activity following methylphenidate 17.5-56 mg/kg (p.o.) and following amphetamine at 10 mg/kg.

* Drug discrimination between atomoxetine and cocaine in rats trained to discriminate 10 mg/kg cocaine showed partial generalization of atomoxetine to cocaine at a dose range of 0.25-50.0 mg/kg atomoxetine. Maximum substitution (77%) at the highest dose

* Drug discrimination between atomoxetine and cocaine in monkeys trained to discriminate 0.4 mg/kg cocaine showed generalization of atomoxetine to cocaine at the following atomoxetine doses:

Monkey A	1.0 mg/kg
Monkey B	10.0 mg/kg
Monkey C	0.32, 10.0 mg/kg (not 1.0 or 3.2 mg/kg)
Monkey D	no generalization

Protocol proposal:
Effects of atomoxetine in cocaine-trained rhesus monkeys under concurrent schedules of IV drug self-administration and food presentation

* Monkeys will be trained in a two-lever test box to associate one lever with IV injection of cocaine and the other lever with delivery of food. Reinforcement will be on an FR30 schedule of reinforcement.

* Test drugs: methylphenidate (0.003 - 0.32 mg/kg), d-amphetamine (0.001 - 0.032 mg/kg), the norepinephrine reuptake inhibitor desipramine (0.01 - 0.32 mg/kg) and atomoxetine (0.01 - 0.32 mg/kg).

* Well-designed study with one concern: no information is provided describing how data will be analyzed.

Protocol proposal:
Effects of atomoxetine in rhesus monkeys trained to self-administer cocaine.

* Monkeys will be trained to barpress for a training dose of IV cocaine (between 0.01 and 0.10 mg/kg) on an FR25 schedule of reinforcement.

* Test drugs: methylphenidate, the norepinephrine reuptake inhibitor desipramine and atomoxetine. Doses will range between a dose low enough not to maintain responding and a dose high enough to suppress responding below saline levels.

* Well-designed study with appropriate data analysis.

* **CSS recommendation: consider addition of phentermine as comparator in the self-administration studies**

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/s/

Anna-Marie Homonnay
5/21/02 10:56:28 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-411

Eli Lilly and Company
Attention: Rex Souter, Ph.D.
Sr. Regulatory Research Scientist
Lilly Corporate Center
Indianapolis, Indiana 46285

Dear Dr. Souter:

Please refer to the meeting between representatives of your firm and FDA on February 20, 2002. The purpose of the meeting was to provide FDA requirements for the assessment of abuse potential for atomoxetine hydrochloride.

We acknowledge receipt of your meeting minutes dated March 14, 2002.

We also refer to our April 16, 2002, communication regarding our comments for the LYBO study provided to you by the FDA Controlled substances Staff.

The official minutes of that meeting are enclosed. We wish to clarify the point that FDA will take all data into consideration when making labeling and any scheduling recommendation, not just the LYBO study results.

If you have any questions, call Ms. Anna Marie Homonnay, Regulatory Health Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

Homonnay Weikel, Anna M

From: Baweja, Raman K
Sent: Thursday, November 07, 2002 5:16 PM
To: Laughren, Thomas P; Homonnay Weikel, Anna M
Cc: Baweja, Raman K
Subject: NDA 21,411, Atomoxetine HCl, Strattera - Biopharm Issues

Tom

I am providing you a scientific write-up for two Biopharm issues regarding responses from the sponsor for Atomoxetine Hydrochloride capsules. The write-up is slightly detailed so that it'll give you a clear idea.

For the action letter please edit and condense as you see best, particularly regarding item 2 below, viz., the Biopharmaceutics Classification System (BCS) issue.

1) The sponsor has agreed to adopt the dissolution method and specification that the Agency had proposed to them, for all strengths of atomoxetine HCl capsules (5,10, 18, 25, 40 and 60 mg) capsules: [USP Apparatus II (paddle) at 50 rpm; 1000 ml of 0.1 N HCl at 37 degrees; Q = — in 30 minutes]. So, this issue is settled.

2) (a) Biopharmaceutics Classification System (BCS). We had written to them the following..... "Although, atomoxetine hydrochloride is highly soluble and highly permeable, the slower release of the highest strength (60 mg) capsule in pH 6.8 buffer (— % in 30 minutes) does not meet the criteria for being classified as a BCS Class 1 drug *product*."

They mention that based on the properties of the drug, it should qualify as a BCS 1 drug.

To be classified as a BCS 1 drug, three (3) entities have to qualify separately and distinctly as the scrutiny is on both the drug substance **and** on the drug product. These are:

(i) solubility..... and as a drug substance atomoxetine is highly soluble;
(ii) permeability .....the drug is highly permeable and the review has assessed that;
(iii) dissolution..... this is a test on the drug *product (emphasize drug 'product')*, and for an immediate release drug product to be considered rapidly dissolving, —% of the drug should dissolve within 30 minutes in pH ranging media from pH 1 to pH 6.8. We have conveyed to them that the slower release of the highest strength (60 mg) capsule in pH 6.8 buffer (— % in 30 minutes) does not meet the criteria for being classified as a BCS Class 1 drug *product*.'

b) They mention that a bioequivalent (BE) study showed that 60 mg capsule was BE to (40 mg + 20 mg) capsules; this is a linkage issue not a BCS one. For BCS then, it is a combination of solubility, permeability, and dissolution issues. The sponsor does not make it on dissolution for the 60 mg highest strength capsule in pH 6.8 buffer.

Please let the sponsor know in the action letter that the Agency does not consider atomoxetine hydrochloride to be a BCS class 1 drug.

Thank you

Ray

Homonnay Weikel, Anna M

From: Khin, Ni Aye
ent: Thursday, December 13, 2001 9:40 AM
.o: Homonnay Weikel, Anna M; Glass, Roberta L; Shen, Yuan Li
Subject: Inspection sites for atomoxetine

Hi all,

I have received a list of investigators from Rex Souter, Lilly. My understanding for this NDA is that it included both adult and peds indication; as well as qd and bid dosing. We are thinking of inspecting 3 sites each for adult and peds. For adult 3 sites, 2 from LYAO and 1 from LYAA or vice versa. For Peds 3 sites, it will include 2 for bid dosing (LYAC) and 1 for qd (LYAT). As per my conversation with Roberta, because of the age range of peds studies (7-12 yrs for HFBD/HFBK vs 8-18 yrs for LYAC), we are thinking of not including sites for 7-12yrs studies (HFBK and HFBD). Could you please let me know ASAP if there is a particular site of interest (eg. outliers) in any of these studies. I will get back to you all, with a suggestion list of sites for inspection after checking the inspection history of investigators and number of subjects enrolled/discontinued at each site. Thanks.

--Ni

Gill-Sangha, Gurpreet

From: Gill-Sangha, Gurpreet
Sent: Wednesday, July 31, 2002 3:25 PM
To: 'miller_mary_barbara_g@lilly.com'
Cc: Oliver, Thomas F; Gill-Sangha, Gurpreet
Subject: Agency's Meeting Minutes for CMC telecon July 15, 2002

Mary Barbara Miller:
Attached is the Agency's version of our conference call meeting minutes with Lilly dated July 15, 2002 to discuss CMC issues for the Lilly application, NDA 21-411. Please note that these minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

Regards,
Gurpreet Gill-Sangha, Ph.D.
Review Chemist

Homonnay Weikel, Anna M

From: Rosloff, Barry N
Sent: Thursday, November 14, 2002 5:46 PM
To: Homonnay Weikel, Anna M; Laughren, Thomas P
Cc: Elayan, Ikram; Rosloff, Barry N
Subject: FW: Responses from Pharm tox for atomoxetine

Here are the pharm/tox conclusions. As you can see, we are agreeing with the sponsor's plan to qualify impurity [redacted]. Regarding the labeling, Ikram has included the sponsor's reasons for wanting changes from our previous version, and our reasons for not making those changes we don't agree with. (We might note in our letter that we did adopt many of the sponsor's changes).

Barry

-----Original Message-----
From: Elayan, Ikram
Sent: Thursday, November 14, 2002 10:52 AM
To: Rosloff, Barry N
Subject: Responses from Pharm tox for atomoxetine

Here is the attachment for atomoxetine

Pharmacology and Toxicology re...

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

epartment of Health and Human Services
ublic Health Service
ood and Drug Administration

Request for Consultation

Date: 1/11/2002 Rothmann

To: HFD-710/Jin/~~RKelly~~ From: Neuropharmacology, HFD-120

IND/NDA No. NDA 21-411

Drug Name atomoxetine

Trade Name

Sponsor Lilly

Indication ADHD

Type of Document new NDA

Date of Document 10/11/2001

Reason for Request

The pharm/tox reviewer has requested a statistical review of the carcinogenicity data. This is an electronic submission so I will forward the link.
e PDUFA due date is 8/11/02.

Thank you

Signature of Requester	Method of Delivery (Check One) ( ) Mail ( ) Hand
Signature of Receiver	Signature of Deliverer