

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-411**

**ADMINISTRATIVE DOCUMENTS**

# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-411	Efficacy Supplement Type SE-	Supplement Number
Drug: Strattera (atomoxetine HCl) Capsules		Applicant: Lilly Research Laboratories
RPM: Weikel		HFD-120 Phone # 594-5535
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		IS
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		11/26/02
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input type="checkbox"/> No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified
❖ Exclusivity Summary (approvals only)		√
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)		none

<b>General Information</b>	
<b>❖ Actions</b>	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	First review cycle 8/12/02
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
<b>❖ Public communications</b>	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
<b>❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))</b>	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	√
• Most recent applicant-proposed labeling	√
• Original applicant-proposed labeling	na
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)	√
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	na
<b>Labels (immediate container &amp; carton labels)</b>	
• Division proposed (only if generated after latest applicant submission)	na
• Applicant proposed	
• Reviews	
<b>❖ Post-marketing commitments</b>	
• Agency request for post-marketing commitments	√ see pharm/tox
• Documentation of discussions and/or agreements relating to post-marketing commitments	√
<b>❖ Outgoing correspondence (i.e., letters, E-mails, faxes)</b>	
<b>❖ Memoranda and Telecons</b>	
<b>❖ Minutes of Meetings</b>	
• EOP2 meeting (indicate date)	√
• Pre-NDA meeting (indicate date)	√
• Pre-Approval Safety Conference (indicate date; approvals only)	deferred
• Other	
<b>❖ Advisory Committee Meeting</b>	
• Date of Meeting	NA
• 48-hour alert	NA
<b>❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)</b>	
NA	

<b>Clinical and Summary Information</b>	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	√
• Clinical review(s) <i>(indicate date for each review)</i>	√
• Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>	See chem review
• Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	√
• Pediatric Page (separate page for each indication addressing status of all age groups)	√
• Statistical review(s) <i>(indicate date for each review)</i>	√
• Biopharmaceutical review(s) <i>(indicate date for each review)</i>	√
• Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i>	√
• Clinical Inspection Review Summary (DSI)	
• Clinical studies	√
• Bioequivalence studies	NA
<b>CMC Information</b>	
• CMC review(s) <i>(indicate date for each review)</i>	√
• Environmental Assessment	
• Categorical Exclusion <i>(indicate review date)</i>	NA
• Review & FONSI <i>(indicate date of review)</i>	NA
• Review & Environmental Impact Statement <i>(indicate date of each review)</i>	NA
Micro (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>	NA
• Facilities inspection (provide EER report)	Date completed: not completed yet (√) Acceptable ( ) Withhold recommendation
• Methods validation	( ) Completed (√) Requested ( ) Not yet requested
<b>Nonclinical Pharm/Tox Information</b>	
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	√
• Nonclinical inspection review summary	NA
• Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	√
• CAC/ECAC report	√

NDA ACTION LETTER ROUTING RECORD

NDA#: 21-411

Date Received: 8/8/02

Drug: Strattera (atomoxetine)

Division: HFD- 120

Type of Letter: AP (AE) NA

Drug Classification: 15

Patent Info Received: ✓

Safety Update: requested in AE letter

Phase IV Commitment: requested in AE letter

LEWER

RECEIPT

ACTION

Colleen LoCicero  
Linda Carter  
Special Assistant  
to the Director

Date 8/8/02 Initials /S/ Date 8/8/02 Initials /S/

Comments:

- It does not appear that an EA was done.
- Carton + container labels follow sponsor proposed pi under tab B.
- EER was completed 8/5.
- Refer to TOC for location of reviews, labels, minutes, etc. (eopz meeting minutes are included - see E)
- DSRES review indicates ~~DPMA~~ review - ppi - dia may review pi?

Chemistry Review

Date 8.8.02 Initials /S/ Date 8.8.02 Initials /S/

Comments:

Several CMC deficiencies to be addressed. CCS issue remains unresolved for on-site. EA ok categorical exclusion as noted in review 2. Labeling issue re: ~~active~~ name to be confirmed. Note changes in new or draft letter.

Pharmacology &  
Toxicology Review

Date \_\_\_\_\_ Initials \_\_\_\_\_ Date \_\_\_\_\_ Initials \_\_\_\_\_

Comments:

R. Temple, M.D.  
Director, Office of  
Drug Evaluation I

Date 8/9/02 Initials /S/ Date \_\_\_\_\_ Initials \_\_\_\_\_

Returned to Division for  
Corrections \_\_\_\_\_ Forwarded \_\_\_\_\_

Letter Signed \_\_\_\_\_

Comments:

EXCLUSIVITY SUMMARY for NDA # 21-411

Trade Name Strattera® Capules  
Generic Name atomoxetine hydrochloride

Applicant Name Eli Lilly Company HFD- 120  
Approval Date \_\_\_\_\_

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES /  / NO /  /

b) Is it an effectiveness supplement? YES /  / NO /  /

If yes, what type (SE1, SE2, etc.)? \_\_\_\_\_

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES /  / NO /  /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

\_\_\_\_\_  
\_\_\_\_\_

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

\_\_\_\_\_  
\_\_\_\_\_

d) Did the applicant request exclusivity?

YES /  / NO /  /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e Has pediatric exclusivity been granted for this Active Moiety?

YES /  / NO /  /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /  / NO /  /

If yes, NDA # \_\_\_\_\_ Drug Name \_\_\_\_\_

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /  / NO /  /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / \_\_\_ / NO / X /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # \_\_\_\_\_

NDA # \_\_\_\_\_

NDA # \_\_\_\_\_

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / \_\_\_ / NO / \_\_\_ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # \_\_\_\_\_  
NDA # \_\_\_\_\_  
NDA # \_\_\_\_\_

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.**

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /\_\_\_/ NO /\_\_\_/

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /\_\_\_/      NO /\_\_\_/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

\_\_\_\_\_

\_\_\_\_\_

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /\_\_\_/      NO /\_\_\_/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /\_\_\_/      NO /\_\_\_/

If yes, explain: \_\_\_\_\_

\_\_\_\_\_

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /\_\_\_/ NO /\_\_\_/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # \_\_\_\_\_

Investigation #2, Study # \_\_\_\_\_

Investigation #3, Study # \_\_\_\_\_

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /\_\_\_/ NO /\_\_\_/

Investigation #2 YES /\_\_\_/ NO /\_\_\_/

Investigation #3 YES /\_\_\_/ NO /\_\_\_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
 NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
 NDA # \_\_\_\_\_ Study # \_\_\_\_\_

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1                      YES /\_\_\_/                      NO /\_\_\_/  
 Investigation #2                      YES /\_\_\_/                      NO /\_\_\_/  
 Investigation #3                      YES /\_\_\_/                      NO /\_\_\_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
 NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
 NDA # \_\_\_\_\_ Study # \_\_\_\_\_

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #\_\_, Study # \_\_\_\_\_  
 Investigation #\_\_, Study # \_\_\_\_\_  
 Investigation #\_\_, Study # \_\_\_\_\_

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
IND # \_\_\_\_\_ YES /\_\_\_/ ! NO /\_\_\_/ Explain: \_\_\_\_\_  
! \_\_\_\_\_  
! \_\_\_\_\_  
!

Investigation #2 !  
IND # \_\_\_\_\_ YES /\_\_\_/ ! NO /\_\_\_/ Explain: \_\_\_\_\_  
! \_\_\_\_\_  
! \_\_\_\_\_  
!

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !  
YES /\_\_\_/ Explain \_\_\_\_\_ ! NO /\_\_\_/ Explain \_\_\_\_\_  
! \_\_\_\_\_  
! \_\_\_\_\_  
!

Investigation #2 !  
YES /\_\_\_/ Explain \_\_\_\_\_ ! NO /\_\_\_/ Explain \_\_\_\_\_  
! \_\_\_\_\_  
! \_\_\_\_\_  
!

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /\_\_\_/                      NO /\_\_\_/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Signature of Preparer: Anna Marie H. Weikel

Title: Regulatory Health Project Manager

\_\_\_\_\_  
Signature of Office of Division Director

\_\_\_\_\_  
Date

cc:

Archival NDA  
HFD-120/Division File  
HFD-120/Homonnay  
HFD-093/Mary Ann Holovac  
HFD-104/PEDS/T.Crescenzi

Form OGD-011347

Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

# PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

## PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA 10/11/01. Application Written Request was made to: NDA/IND#             
 Timeframe Noted in Written Request for Submission of Studies 10/17/04  
 NDA# 211111 Supplement #            Choose one: SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8 SLR  
 Sponsor             
 Generic Name            Trade Name             
 Strength            Dosage Form/Route Oral capsule  
 Date of Submission of Reports of Studies 11/12/01  
 Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies) 11/12/02  
Jan 12, 2002

Was a formal Written Request made for the pediatric studies submitted?	Y <input checked="" type="checkbox"/>	N <input type="checkbox"/>
Were the studies submitted after the Written Request?	Y <input checked="" type="checkbox"/>	N <input type="checkbox"/>
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y <input checked="" type="checkbox"/>	N <input type="checkbox"/>
Was the timeframe noted in the Written Request for submission of studies met?	Y <input checked="" type="checkbox"/>	N <input type="checkbox"/>
If there was a written agreement, were the studies conducted according to the written agreement? OR If there was no written agreement, were the studies conducted in accord with good scientific principles?	Y <input checked="" type="checkbox"/>	N <input type="checkbox"/>
Did the studies fairly respond to the Written Request?	Y <input checked="" type="checkbox"/>	N <input type="checkbox"/>

SIGNED           / S /           DATE 11/28/01  
 (Reviewing Medical Officer)

Do not enter in DFS - FORWARD TO PEDIATRIC EXCLUSIVITY BOARD, HFD-960.

## PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity       **Granted**       **Denied**

Existing Patent or Exclusivity Protection:

NDA/Product #	Eligible Patents/Exclusivity	Current Expiration Date
<u>          </u>	<u>5,105,590</u>	<u>11 JAN 2015</u>
<u>          </u>	<u>10,000,000</u>	<u>17 SEP 2018</u>
<u>          </u>	<u>12,184,000</u>	<u>17 SEP 2018</u>

SIGNED           / S /           DATE 12/18/01

**BEST POSSIBLE COPY**

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

-----  
Terrie Crescenzi  
12/18/01 03:57:49 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 21-411 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: \_\_\_\_\_

Stamp Date: 10.12.01 Action Date: 11.26.02

HFD: 120 Trade and generic names/dosage form: Strattera (atomoxetine HCl) Capsules

Applicant: Eli Lilly Therapeutic Class: 1S

Indication(s) previously approved: Treatment of ADHD

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of ADHD

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply:  Partial Waiver  Deferred  Completed  
NOTE: More than one may apply  
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

cc: NDA  
HFD-950/ Terrie Crescenzi  
HFD-960/Grace Carmouze  
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960  
301-594-7337

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

Indication =2: \_\_\_\_\_

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

cc: NDA  
HFD-960/ Terrie Crescenzi  
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960  
301-594-7337

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Anna-Marie Homonnay  
11/22/02 12:04:34 PM

## BRIEF MEETING MINUTES

Date: February 20, 2002  
NDA: 21-411  
Location: Woodmont II, Conference Room E  
Firm: Eli Lilly  
Drug: atomoxetine hydrochloride  
Indication: attention deficit disorder  
Participants:

### FDA:

Robert Temple, MD, Director, ODE I and Associate Director for Medical Policy

### Division of Neuropharmacological Drugs

Russell Katz, MD, Director  
Thomas Laughren, MD, Teamleader, Psychiatric Drugs  
Roberta Glass, MD, Medical Reviewer  
Anna Marie Homonnay, R.Ph., Regulatory Health Project Manager

### Controlled Substances Staff (CSS)

Deborah Leiderman, MD, Director  
Ann-Kathryn Maust, MD, Reviewer  
Mike Klein, PhD, Reviewer  
Katherine Bonson, PhD, Reviewer  
Corinne Moody, Project Manager

### Eli Lilly and Company

Albert Allen, MD, PhD  
Gregory Brophy, PhD, Director, US Regulatory Affairs  
David Clarke, PhD, Toxicologist  
Douglas Faries, PhD, Statistician  
J. David Leander, PhD, Lilly Research Fellow, Neuroscience Research  
David Michelson, MD, Atomoxetine Medical Director  
Anne Nobles, JD, Atomoxetine Team Leader  
Rex Souter, PhD, US Regulatory Scientist

#### BACKGROUND:

Lilly requested this meeting with FDA to clarify the requirements for the assessment of atomoxetine abuse potential and to reach agreement on what will constitute a sufficient body of evidence that the drug does not possess abuse potential. A comprehensive briefing package dated January 29, 2002, was submitted to the Agency. The discussion focused on the proposals outlined in the briefing document.

#### DISCUSSION:

Dr. Leiderman clarified to Lilly the CSS concerns about the abuse potential data package submitted in the NDA. She pointed out several weaknesses in the pre-clinical and clinical data and indicated a strong need for a repeat clinical abuse potential study. She stressed that the completed LYAD study did not answer the questions sufficiently due to the study results and design issues. She added that the proposed LYBO study may answer the question, with some additional CSS input about the design. In addition, although the monkey studies were well designed, they will not be necessary since another clinical abuse liability study (LYBO) is planned and should be sufficient.

Dr. Leiderman said that the primary CSS concerns about the design of the LYAD abuse potential study were the heterogeneous patient population of recreational drug users, the choice of drug comparators, the failure of methylphenidate to distinguish sufficiently from placebo, and the doses of atomoxetine employed in the study (see attached slide on clinical abuse liability study LYAD for additional CSS comments). In addition, the CSS noted several instances of drug diversion and overdose that occurred in the clinical trials and require explanation. The CSS felt that the LYBO study could better answer the question since the patient population would consist of stimulant abusers; however, the protocol would need a few additional changes, such as, the choice of comparators and the doses of atomoxetine employed.

The CSS suggested Lilly use methylphenidate and phentermine, a Schedule IV stimulant, as comparators. Desipramine was also discussed. Lilly's consultant had concerns about 'noradrenergic noise' with phentermine but agreed to consider it. Lilly also expressed concerns about multiple comparisons and suggested that the comparison to placebo should be designated as the primary outcome based upon drug profiles. Lilly tentatively proposed using the Liking scales of the visual analog scale scores and the MBG subscales from the ARCI, but pointed out that this may be difficult due to the atomoxetine dose response curve. Atomoxetine doses of 40 mg, 90 mg and 180 mg were selected and initially agreed upon. It was agreed that Lilly would put forth a more definitive proposal.

A list of questions about the clinical data submitted in the NDA, LYAD study and other clinical studies, was supplied to Lilly during the meeting and Lilly agreed to provide responses to these requests.

Both FDA and Lilly presented conclusions about the results of the pre-clinical studies and the LYAD abuse potential clinical trial for further discussion.

Lilly committed to performing a second human abuse potential study, LYBO, after revising the protocol, but also emphasized that they would need assurance from FDA about the data analysis of the study results and the conclusions that are drawn by FDA regarding the controlled substance status of atomoxetine.

Lilly further noted that although they cannot prove the null hypothesis with this type of study, they could show a lack of a body of evidence for abuse potential of atomoxetine. Lilly stressed that individual data would not be the best way to approach the analysis of an abuse potential study but rather the focus should be on group data and overall study trends. Lilly characterized the adverse findings in the LYAD study as 'noise'.

Lilly expressed concerns about the timing of the completion of the study with respect to FDA taking an action on the pending NDA. FDA said that completing the study post-marketing was not an option and agreed to move as expeditiously as possible with the review of a new proposal.

In order to reach agreement about the design, including analysis plan and outcome measures, it was agreed that Lilly would submit a revised protocol for study LYBO including a well-defined statistical analysis plan for FDA CSS review. FDA also committed to review the proposal as expeditiously as possible.

**Attachments:**

Slides on LYAD study

List of clinical abuse potential questions provided during meeting

CSS Slides:

**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.

### Questions for Sponsor Regarding 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.

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Russell Katz  
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## BRIEF MEETING MINUTES

Date: March 6, 2001

IND: —

Location: Woodmont II, Conference Room E

Firm: Lilly Research Labs

Drug: atomoxetine HCl

Indication: attention deficit disorder

Participants:

FDA ODE I:

Saul Sobel, MD, Deputy Director ORM

Russell Katz, MD Division Director

Thomas Laughren, MD Clinical Teamleader, Psychiatric Drugs

Judy Racoosin, MD. Clinical Safety Team Leader

Roberta Glass, MD Medical Reviewer

Kun Jin, PhD, Biostatistics Teamleader

Yuan Li Shen, PhD, Biostatistician

Barry Rosloff, PhD, Pharmacology/Toxicology Teamleader

Anthony Proakis, PhD, Pharmacologist (from Division of Cardio-Renal Drugs)

Ray Baweja, PhD, Biopharmaceutics Teamleader

Ifthekar Mahmood, PhD, Biopharmaceutics Reviewer

Anna Marie Homonnay, RPh, Regulatory Health Project Manager

Lilly:

Gregory Brophy, PhD, Director, US Regulatory Affairs

Douglas Faries, PhD, Statistician

David Michelson, MD, Atomoxetine Medical Director

Anne Nobles, JD, Atomoxetine Team Leader

Rex Souter, PhD, US Regulatory Scientist

Holly Thomasson, MD, PhD, Clinical Pharmacologist

Gary Tollefson, MD, PhD, Distinguished Lilly Research Scholar

J.F. Wernicke, MD, PhD

**BACKGROUND:** The objective of the meeting was to provide further guidance on Lilly's proposals for clinical safety data to support the safety of atomoxetine HCl in 2D6 poor metabolizers, as detailed in the February 19, 2001, briefing document. A previous EOP2 type meeting took place on February 8, 2000. The discussion mainly focused on a list of specific questions (as delineated and summarized below) which were provided in the briefing document; although, FDA raised some issues of concern also. Lilly expects to make an NDA submission sometime in the fourth quarter of this year.

## DISCUSSION:

Cardiovascular results – QTc evaluation: Lilly will present data to support the safety of atomoxetine with respect to cardiac repolarization, including QTc/plasma concentration relationships.

Clinical data to support assessment of safety in 2D6 poor metabolizers (PMs) throughout the proposed dose range: It has been previously agreed that safety data from approximately 100 PM children (including some extensive metabolizers (EMs) pharmacologically converted with fluoxetine to PMs) dosed at the upper end of the dose range would be acceptable. The briefing document addresses the sources of the PM exposures, as well as, anticipated dosing for EMs and PMs. A primary objective of the meeting is to seek agreement that the PM strategy to be outlined has adequately fulfilled FDA expectations around exposures to the upper end of the atomoxetine dose range.

- Lilly began with a brief presentation in response to an FDA question about the total number of PMs that will be ultimately included in the NDA submission. Lilly estimated that approximately 100 PMs (status obtained through genotyping) will have been studied in the key clinical studies supplemented with 20 additional PMs from the adult study and 30-40 additional patients from the clinical pharmacology studies. FDA acknowledged that study LYBB included a large number of patients who will have received peak ECGs, including 30-60 PMs. Lilly noted that the PMs are not expected to exhibit large fluctuations in plasma levels at steady-state, thus getting assessments at T<sub>max</sub> is not so critical. Lilly plans to use a baseline QT correction, and this is acceptable. FDA agreed that their planned program will likely include sufficient PMs to adequately characterize the QT effects in PMs.
- FDA referred to a finding in study LYAE of a maximum mean QTc prolongation of 15-17 msec in PMs. Lilly responded that this may have been an aberration and has not been found to reoccur in any subsequent studies.
- FDA asked about the metabolic fate of atomoxetine and Lilly responded that the primary pathway is through 2D6 yielding two metabolites one of which (4-hydroxy metabolite) is modestly active.
- FDA agreed that the proposed 1.2 mg/kg/day threshold for the upper dose range was appropriate.
- FDA also asked that an explanation be provided for several cases of appendicitis which had been observed and a comparison with the known background rate.

Clinical data for the NDA submission: Lilly is developing plans regarding the cutoff for inclusion of data in the ISS and ISE. These data will include all ICH required exposures. Lilly would like to determine whether FDA agrees with this proposal.

- FDA inquired about the number of patients to be studied at the therapeutic dose for six months. Lilly responded that around 400-600 patients will be studied for six months at the 1 mg/kg/day dosage, and above, for the original submission, and that these numbers will be supplemented with additional patients through the safety update. It was noted that the planned exposures should be adequate.

Once-daily dosing: Lilly believes that it is likely that many clinicians and patients will be interested in information concerning the efficacy of one-daily dosing. Study LYAT was submitted to the IND on October 19, 2000, to assess the efficacy of once-daily treatment with atomoxetine. Lilly plans to include information about the efficacy of once-daily dosing in labeling based upon the results of this study. Lilly seeks concurrence that FDA would support inclusion of information about once-daily atomoxetine dosing in labeling based on the demonstration of efficacy in this single placebo controlled study.

- FDA agreed with the proposal but recommended obtaining additional PK information on once daily dosing through either a population PK technique or a formal study.

Inclusion in labeling of information from secondary measures and inclusion in labeling of information relative to methylphenidate:

FDA advised that our current approach is to allow secondary outcomes under certain fairly strict conditions. A company still has to identify a primary outcome (or outcomes) in the protocol, and it will succeed or fail based on the results for these outcomes. If there is more than one, it must make it at 0.05 on each. However, if a sponsor wants to declare, up front in the protocol, one or more secondary outcomes as key secondary outcomes for consideration, we will consider this. We must agree in advance with the sponsor that each is a legitimate and clinically relevant outcome. Then, the sponsor must set up a plan for testing the secondary outcomes on a conditional basis, i.e., if they make it on the primary, they then will have 0.05 for testing the key secondaries (the 0.05 could be split over the secondaries, or it could be sequential testing, with 0.05 at each level). They will then be able to describe in clinical trials those key secondaries for which they have achieved statistical significance. However, one additional requirement is for replication, i.e., it is not sufficient to make it on a particular key secondary outcome in only one trial.

- Lilly inquired whether or not FDA would consider depressive symptoms to be an acceptable secondary outcome. FDA commented that such a measure would constitute a separate claim, and it would not be acceptable to approach such a claim in so casual a manner. A separate program would be needed.
- Regarding the question of comparative claims, FDA did not rule out such claims, but as with secondary outcomes, indicated that this would require great care in study design and statement of hypotheses for testing.

Priority review consideration: Lilly views atomoxetine as a candidate for a priority review based upon lack of abuse potential.

- FDA will take this under consideration but would like to reserve the final judgement until the application has been filed.

**ACTION ITEMS:**

Lilly is planning to request a formal pre-NDA meeting later this year.

Signature, minutes preparer: \_\_\_\_\_

*/s/*  
Anna M. Homonnay-Weikel, R.Ph.  
Regulatory Health Project Manager

Concurrence, Chair: \_\_\_\_\_

*/s/*  
Thomas Laughren, M.D.  
Teamleader, Psychiatric Drugs

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Thomas Laughren  
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## BRIEF MEETING MINUTES

**Date:** February 8, 2000

**IND:** \_\_\_\_\_

**Location:** Woodmont II, Conference Room E

**Firm:** Lilly Research Laboratories

**Drug:** tomoxetine HCl

**Indication:** pediatric and adult attention deficit disorder

### Participants:

#### FDA:

Russell Katz, MD Director

Thomas Laughren, MD, PDP Teamleader

Roberta Glass, MD, Medical Reviewer

Glenna Fitzgerald, PhD, Pharmacology/Toxicology Teamleader (absent)

Ifthekar Mahmood, PhD, Biopharmaceutics Reviewer

Anna M. Homonnay-Weikel, RPh, Regulatory Project Manager

#### Lilly Research Laboratories:

Gregory Brophy, PhD, Director, US Regulatory Affairs

David Clark, PhD, Toxicologist

Douglas, Faries, PhD, Statistician

David Michelson, MD, Tomoxetine Medical Director

Anne Nobles, JD, Tomoxetine Team Leader

Rex Souter, PhD, US Regulatory Scientist

Holly Thomasson, MD, PhD, Clinical Pharmacologist

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### BACKGROUND:

The objective of the meeting was to provide further guidance on Lilly's proposed Phase III clinical development plans for dosing recommendations, clinical safety, and clinical pharmacology program for tomoxetine HCl for the treatment of pediatric and adult attention deficit disorder. A previous EOP2 type meeting took place on January 20, 1999.

### DISCUSSION:

- The meeting began by Lilly summarizing the clinical experience with this product for ADHD, including present clinical development status, and their proposed clinical plans (please see attached overheads).

- Lilly's approach for assessing dose range, as detailed in the briefing package, was presented and discussed. FDA requested that the pediatric ADHD dose response trial be enriched with approximately 100 CYP2D6 poor metabolizers (PMs) at the higher doses, since the feeling is that the currently proposed safety database would be insufficient to support the proposed upper dose range in pediatric PMs due to concerns about the profound differences in the pharmacokinetics in these patients resulting from CYP2D6 inhibition. Alternatively, concomitant administration of a 2D6 inhibitor to normals would also be an acceptable approach for obtaining sufficient numbers of PMs for enrichment purposes. Having a requirement in labeling for monitoring plasma levels in patients needing more than an initial low target dose was an alternative proposal for addressing this issue.
- It was agreed that the proposal to bridge safety data from adults to children, as detailed in the briefing package, would provide adequate support for the proposed pediatric dose response study (LYAC).
- It was agreed that the proposed biopharmaceutical plan was acceptable including the proposed drug interaction studies. Lilly indicated that the drug interaction program was based upon in vitro studies and should generalize to other drugs which may be taken concomitantly with tomoxetine.
- It was agreed that the proposed adult study, LYAA, was acceptable by design and would be generalizable to the intended population; however, it is probable that the PDAC will be consulted during the review due to the novelty of this indication in the adult population. In addition, input by the division statisticians has not been obtained yet.
- Whether the proposed plans for clinical safety exposure for pediatric and adult ADHD patients, as detailed in the briefing package, would be adequate to support registration would depend on whether there is compelling evidence presented that the pharmacokinetic properties of the drug are similar between adults and children, and on the relevance of the doses previously studied in past adult depression trials to the currently proposed doses. However, the Division would prefer to see more acute exposures in the pediatric population, based on ICH guidelines, since that is viewed as the predominant population for this disorder.
- FDA indicated that in order for a priority review to be granted, a distinct benefit in terms of tolerance and efficacy compared to marketed products must be shown. Lilly felt that the potential lack of abuse potential for drugs in this class, particularly in the adolescent and adult populations, may qualify a priority review. However, as per the CDER priority review policy, this decision is usually deferred until the application is accepted for filing.

- It was agreed that this application may qualify for pediatric exclusivity under FDAMA. Lilly is encouraged to submit a proposed pediatric study request, in accordance with the CDER guidance for industry on pediatric exclusivity. In addition, the Pediatric Written Request must be issued prior to NDA submission of the completed pediatric studies reports in order to qualify for pediatric exclusivity.

Signature, minutes preparer: \_\_\_\_\_  
Anna M. Homonnay-Weikel, RPh  
Regulatory Project Manager

Concurrence : \_\_\_\_\_  
Thomas Laughren, M.D.  
Clinical Team leader, Psychiatric Drugs

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HFD-120/Glass  
HFD-860/Mahmood  
HFD-120/Homonnay

MEETING MINUTES

## MEMORANDUM OF MEETING MINUTES

**IND:** —

**DRUG:** Tomoxetine Hydrochloride

**SPONSOR:** Lilly Research Laboratories

**DATE/TIME:** January 20, 1999

**LOCATION:** Woodmont Building\Conference Room E

### **FDA ATTENDEES:**

Russell Katz, M.D., Acting Division Director (absent)  
Thomas Laughren, M.D., Psychiatric Drugs Teamleader  
Roberta Glass, M.D., Medical Reviewer  
Glenna Fitzgerald, Ph.D., Pharmacology/Toxicology Teamleader  
Barry Rosloff, Ph.D., Pharmacologist  
Kun Jin, Ph.D., Biostatistics Teamleader  
Richard Chen, Ph.D., Biostatistician  
Iftekhhar Mahmood, Ph.D., Clinical Pharmacologist  
Anna M. Homonnay-Weikel, R.Ph., Project Manager

### **LILLY RESEARCH LABORATORIES ATTENDEES:**

Gregory Brophy, Ph.D., Director U.S. Regulatory Affairs  
David Clarke, Ph.D., Toxicologist  
Douglas Faries, Ph.D., Biostatistician  
John Heiligenstein, M.D.  
Douglas Kelsey, M.D.  
William Potter, M.D., Lilly Clinical Research Fellow  
Holly Thomasson, Ph.D., Clinical Pharmacologist  
Jennifer Witcher, Ph.D., Pharmacokineticist  
Rex Souter, Ph.D., US Regulatory Scientist

### **BACKGROUND:**

Lilly had requested the Division's input on their proposed registration plan for tomoxetine hydrochloride for the treatment of pediatric and adult ADHD patients.

## DISCUSSION:

### Pharm/Tox Issues:

- As previously requested (9/12/97 fax), FDA would like to see toxicity studies in juvenile animals which are specifically designed to address the potential effects of drug exposure on growth and maturation; and neurological, behavioral, and reproductive development, to support use in the proposed patient population. These issues would not be sufficiently addressed by standard toxicology studies.
- The protocols in the briefing document are inadequate for the above purposes since reproductive and neurobehavioral evaluations were not included. (Rather, it was indicated that neurobehavioral evaluations would only be done as second tier studies, if considered necessary.) We stated that neurobehavioral evaluations (e.g., a Functional Observational Battery) should be included in the protocols, as should a more detailed than usual histological exam of the nervous system.
- Regarding evaluation of reproductive capacity, the sponsor stated that they plan to do vaginal cytology and sperm exams in the rat study, and this, along with existing data from a segment III study would adequately address this point. We told them to submit a rationale in support of this (as opposed to our suggestion of examining mating and fertility, which in addition to evaluating reproductive capacity, would also evaluate some aspects of neurobehavioral function.) Due to the novelty in this developing area, the division is willing to provide input to revised draft protocols. The protocols should include justifications for ages chosen, study durations, and specific endpoints.

### Clinical Pharmacology Issues:

- The proposed clinical pharm plan appears to be adequate; however, more definitive information is needed about potential drug interactions. Lilly should submit a proposal for drug interaction studies and the results of the CYP2D6 interaction study along with in vitro metabolism data to help determine which drug interaction studies will be necessary and whether any of the data may be extrapolated.
- The Division agreed with Lilly's plan to evaluate only a low strength and a high strength in a bioequivalence study. Dissolution data may be used to waive other strengths provided that the formulations are compositionally proportional.

Clinical Issues:

- Since the FDA views ADHD as primarily a pediatric disorder, two successful clinical trials in this population will be needed. In addition, one successful adult study may be used to extend the claim in the labeling in the 'clinical trials' section.
- Study -HFBE, which includes a discontinuation design, does not meet current FDA policy to qualify as a pivotal study to establish efficacy for short term use; however, the study may support a claim for longer-term efficacy.
- FDA agreed to use of MPH for validation of assay sensitivity in the proposed pivotal studies, -HFBD and -HFBK.
- Safety exposures should approximate ICH guidelines. Prior exposure of adults to tomoxetine in earlier studies could support safety as well. Patients entering the long term safety study who require a medication-free study period will be considered continuously treated for safety purposes; however, may not be included in the total days of exposure count.
- The ADHDRS-IV-Parent:Inv rating instrument is acceptable as the primary efficacy outcome measure for the pediatric studies provided that it is validated.
- FDA requested that the second study include adolescents and girls provided that the preclinical studies support this.
- Although not required, FDA would like to see dose response explored in the clinical trials, if possible.
- It may also be useful to study differential effects between various ADHD subtypes. The exclusion of inattentive subtypes from the clinical trials may be addressed in the labeling.

- Lilly should provide more detail and justifications for the analysis plans. A prospective plan should be developed for addressing decreased enrollment at an individual site, such as, pooling patients.

/s/

Signature, minutes preparer: \_\_\_\_\_

Anna M. Homonnay-Weikel  
Project Manager

/s/

Concurrence, Chair: \_\_\_\_\_

Thomas Laughren, M.D.  
Teamleader, PDP

cc:

Div File

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HFD-120/Laughren/3.17.99/Glass

HFD-120/Fitzgerald/Rosloff/3.16.99

HFD-710/Jin/Chen

HFD-860/Mahmood

HFD-120/Homonnay

MEETING MINUTES

MEMORANDUM

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

DATE: August 14, 2002

FROM: Robert J. Temple, M.D., Director  
Office of Drug Evaluation I, HFD-101

SUBJECT: Atomoxetine, NDA 21-411

TO: File NDA 21-411  
Russell Katz, M.D., Director  
Thomas Laughren, M.D., Team Leader  
Division of Neuropharmacologic Drug Products

It seems useful to summarize available data on QTc and atomoxetine.

A. Pre-clinical data

HERG inhibition and other animal data neither support a problem unequivocally nor reject one. The IC50 of 0.869 mcM is similar to drugs that both are, and are not, prolongers of QTc at therapeutic doses (or even overdose).

B. People with "normal" blood levels of atomoxetine

Effects on QTc in 2D6 EMs and people without "phenotypic" PM, i.e., given 2D6 inhibitors (fluoxetine, paroxetine, quinidine, etc.) plainly have not been seen or, indeed, hinted at, in study LYAE or in the overall (predominantly EM) database. Our sole area of concern is thus people whose blood levels of parent atomoxetine are greatly increased (by about an order of magnitude), i.e., 2D6 poor metabolizers and "phenotypic" PM's, i.e., people on strong 2D6 inhibitors.

C. Data on QTc in PM's

Areas of possible concern include both adults and children/adolescents and we are interested in both mean QTc changes and outliers (although to my best knowledge no drug has ever produced outliers without an effect on mean QTc).

1. Study LYAE

Six PM's were studied in a dose escalation study (0, 30, 45, 60, 75, washout), with each period 5 days and ECGs taken on day 5 at time 0, 1, 2, 4, and 12 hours. The mean QTc changes at each time for each dose, all compared to the placebo value, are:

Time	30 mg	45 mg	60 mg	75 mg
0	2.4	0.3	16.8	14.6
1	-7.5	5.1	0.5	4.5
2	-5.1	-13.3	8	0.7
4	-7.8	10.4	1	10.4
12	-1.3	3.4	-3.3	8.9

A conservative view would be that there may be a 5-10 msec "signal" at 75 mg in PM's (but none at any other time). Mean plasma levels in PM's (n=6) are as shown:

Dose	Cmax	Cav
30	1264	993
45	1868	1504
60	2919	2226
75	3999	3119

It thus seems possible that the signal reflects the higher values attained in the 75 mg group. There are, however, peculiarities of the data that appear to weaken the signal considerably.

The high "0" values, which really are 12 hr trough values (on the 4<sup>th</sup> day of b.i.d. dosing) for the 60 mg and 75 mg doses, seem inexplicable. In PM's, the half life of atomoxetine is 24 hours, so that blood levels one or two hours post-dosing, even if T<sub>max</sub> is 3 hours, cannot be lower than at zero hours (indeed we know from Dr. Boehm's review that 1 and 2 hour values are higher than the zero value), yet QTc at those times are essentially unchanged from placebo.

Dr. Boehm (page 65) shows change in QTc vs. plasma concentration at 0, 1, 2, 4, and 12 hours. One would expect an upward slope for a QT-prolonging drug, but at 1, 2, and 4 hours, overwhelmingly the richest source of data on high blood concentrations (in the 2000-4000 range), there is little or no up-slope, while at 0 and 12 hours there is an up-slope, each largely driven by 3 measurements over 2500 ng/ml (while at 1 hour there were 8 such measurements, at 2 hours 9, and at 4 hours 10). The QT prolongation thus occurs when there were the fewest patients in the high blood level range.

Note that even if one accepts the presence of a signal, in this sequential study, the same people received all doses, so that the same PM population shown sensitive (perhaps) to the QTc-prolonging effect of 75 mg, did not show such an effect at 60 mg, the dose that I believe should be the maximum recommended dose. That could be taken as some reassurance about the safety in PM's of the 60 mg b.i.d. dose.

Finally, although there were only 6 PM's in the study, there were many single observations in which plasma concentrations exceeded 2000 ng/ml (41) or 3000 ng/ml (22), most of them at 1, 2, and 4 hours post-dose. These had no discernable impact on the QTc.

2. Study LYAY

Fifteen patients were given fluoxetine to give them a "phenotypic" PM status, with the following blood levels.

Dose	Cmax	Cav
10	339	252
45	1686	1201
75	2784	1936

It can be seen that the blood levels at the 75 mg dose in LYAY are quite close to the 60 mg values in study LYAE. All agree that study LYAY showed no mean QTc effect, not even a hint and no outliers. In this study (Boehm review, page 70) there were a great many blood levels in the 2000-4000 ng/ml range.

There are thus at 21 adult patients in the two studies who attained blood levels characteristic of PM's given 60 mg. They showed no effect on QTc.

3. HFBJ

In this study of 16 EM, 11 PM, single atomoxetine doses of 10, 30, 60, 90 and 120 mg had no significant QTc effect, nor did repeat doses of 40 mg b.i.d. In all cases the 5-7 msec increase was the same as seen in EMs, probably not reflecting a drug effect, as it is clear that EM's do not have increased QTc with atomoxetine

4. The rest of the data

In general, mean changes are small and inconsistent in clin pharm studies and in phase 2-3 studies, which carried out many ECG evaluations. Although exact timing of ECG's was often variable, that should not matter much with primarily b.i.d. dosing of a drug that (in PM's) has a 24 hour half-life. The above conclusion applies to both adults and children/adolescents. There were almost 300 adolescents and children in placebo-controlled trials, presumably including about 25-30 PM's. Overall, in all studies, there were about 175 PM's. Although there were no mean increased on atomoxetine in QTc, there was some suggestion that PM's had more outliers than EMs.

Conclusion:

Given the order of magnitude increase in blood levels of atomoxetine in PM's and patients given 2D6 inhibitors, even a weak suggestion of a QTc effect needs to be pursued, but I believe there is no evidence of QTc prolongation at a dose of 1.2 mg/kg (still only 60 mg b.i.d. even for a 100 Kg person), despite a fair amount of data that bear on this issue. It is nonetheless reasonable to ask Lilly to bring all available data together in their response to the approvable letter.



Robert Temple, M.D.

cc:  
HFD-101/R Behrman  
HFD-101/R Temple  
draft:sb/8/9/02;8/13/02  
final:sb/8/14/02  
filename:Atomoxetine\_MM\_Aug02.doc

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/s/

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Robert Temple  
8/29/02 06:57:05 PM  
MEDICAL OFFICER

## MEMORANDUM

DATE: August 6, 2002

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

TO: File, NDA 21-411

SUBJECT: Recommendation for Action on NDA 21-411, for the use of Atomoxetine for the treatment of Attention Deficit Hyperactivity Disorder (ADHD)

NDA 21-411, for the use of Atomoxetine, a selective norepinephrine reuptake inhibitor, for the treatment of Attention Deficit Hyperactivity Disorder (ADHD), was submitted by Eli Lilly on 10/11/01. The application contains the results of 6 placebo controlled short-term trials (4 in pediatric patients, 2 in adults). In addition, the sponsor has provided safety experience in over 2500 subjects (350 in clinical pharmacology studies and 2,337 patients in Phase 2/3 studies [including 270 adults]).

The application has been reviewed by Dr. Roberta Glass, efficacy medical reviewer (review dated 6/30/02), Dr. Gerard Boehm, safety team (reviews dated 7/16/02 and 7/25/02), Dr. Judy Racoosin, safety team leader (review dated 7/24/02), Jeanine Best, Division of Surveillance, Research, and Communication Support (patient labeling review dated 7/16/02), Dr. Ni Khin, Division of Scientific Investigations (clinical inspection summary dated 6/26/02), Dr. Gurpreet Gill-Sangha, chemist (reviews dated 7/16/02 and 8/7/02), Dr. Ikram Elayan, pharmacologist (review dated 8/5/02), Dr. Mark Rothman, statistician (mouse carcinogenicity review dated 7/12/02), Drs. Hong Zhao and John Duan, Office of Clinical Pharmacology (review dated 7/25/02), Dr. Ning Li, statistician (review dated 6/14/02), and Dr. Thomas Laughren, Psychiatric Drugs Team Leader (memo dated 7/25/02). Dr. Laughren's memo provides a succinct, comprehensive overview of the data, as well as of the critical issues in the application. The review team recommends that the application be judged Approvable. In this memo, I will briefly review the relevant data, and offer the division's recommendation for action on the application.

### **Effectiveness**

As noted above, the sponsor has provided results of 4 short-term controlled trials in pediatric patients, 2 short-term controlled trials in adults, and 1 long-term controlled trial in pediatric patients.

As described by Drs. Glass, Li, and Laughren, all 6 of the short-term studies yielded clearly statistically significant differences in favor of atomoxetine on their protocol-specified primary outcomes, as well as on many secondary outcomes.

The pediatric studies ranged in duration from 6-9 weeks; the adult studies were each 10 weeks long.

Three of the pediatric studies utilized a flexible dose design; 2 used a range of 10-90 mg/day, given as BID dosing, and one used a titration regimen, starting at 0.5 mg/kg/day, up to 1.5 mg/kg/day, if tolerated; this latter study utilized a once a day dosing regimen. The mean final doses in these studies ranged from 1.3-1.6 mg/kg/day. The remaining pediatric short-term study employed a fixed-dose regimen; patients were randomized to receive either 0.5 mg/kg/day, 1.2 mg/kg/day, 1.8 mg/kg/day, or placebo. In this study, both the mid-and high dose groups were distinguished from placebo, with no evidence of dose-response in these 2 groups.

In the adult studies, patients were randomized to a range of 60-120 mg/day. The mean final dose was 95 mg/day.

It should be noted for the record that in some of the trials, a repeated measures mixed effects model was designated as the primary method of analysis. We have had several discussions with the sponsor about the appropriateness of this analysis (the primary concern of the statisticians has been that this model assumes that missing data are missing at random, an assumption that might not be appropriate). For this reason, we have repeatedly informed the sponsor that we would not ordinarily rely on the results of this analysis. In this application, however, the traditional LOCF analyses were all very positive, and it is on the basis of these results that we have judged the studies to be positive.

## Safety

Dr. Laughren has comprehensively outlined the pertinent safety issues.

The critical consideration with regard to the safety of atomoxetine relates to the fact that it is almost exclusively metabolized by CYP2D6. As the reviewers have noted, about 10% of the Caucasian population is deficient in this enzyme (so-called Poor Metabolizers [PMs]), with the remaining 90% referred to as Extensive Metabolizers [EMs]. The NDA includes data from 136 PMs. In the case of atomoxetine, C<sub>max</sub>'s at steady state in PMs are about 5 times those in EMs, and AUCs and C<sub>ss</sub> avg in PMs are about 7-10 times those in EMs.

Atomoxetine is metabolized by CYP2D6 to an active metabolite, 4-hydroxyatomoxetine, which is rapidly converted to the glucuronide, and renally excreted. After a single 20 mg dose of atomoxetine in EMs, there were 3 circulating species: parent (28%), N-desmethyloxetidine (2%; presumably formed from parent via CYP2C19), and 4-hydroxyatomoxetine-O-glucuronide (71%). The amount of circulating 4-hydroxyatomoxetine was about 6%. The relative percentage of these species circulating in PMs was 70%, 23%, and 8%,

respectively. The level of circulating 4-hydroxyatomoxetine was below the limit of quantification —

After 40 mg BID for 7 days, the C<sub>ss</sub> avg for PMs was 7-8 times greater than in the EMs (other data suggest the factor is 10 times; see Dr. Zhao's review, page 22, Table 8), and the AUC in PMs was about 7 times greater than in EMs. The clearance in PMs is about 10 times slower than in EMs. After single doses, the mean half-life in PMs is about 4 times longer than in EMs (21.6 hours vs 5.2 hours). The C<sub>ss</sub> min is about one half that of the C<sub>ss</sub> max in PMs, and about ¼-1/5 of the C<sub>ss</sub> max in EMs (see Dr. Zhao's review, Table 1, p. 107).

These markedly increased exposures in PMs compared to EMs are presumably responsible for an increased incidence in a number of adverse events in PMs compared to EMs (more on this later). The most worrisome differences seen, though, relate to atomoxetine's possible capacity to prolong the QTc interval in PMs.

Atomoxetine caused 20-30% I<sub>KR</sub> blockade in HERG transfected cells at the maximum plasma levels in EMs and PMs (at the 1.8 mg/kg/day dose), respectively. Atomoxetine also produced a decrease in the duration of the action potential in canine Purkinje cell fibers of 21% at a concentration 45 times the maximum plasma levels in PMs. As Dr. Boehm (pages 58-60) notes, terfenadine also caused a decrease in the action potential duration in canine Purkinje fibers.

To examine the effect of metabolic status on QTc prolongation, the sponsor performed Study LYAE. In this study, 6 PM and 10 EM adults were treated according to the following regimen:

Placebo x 5 days  
Atomoxetine 30 mg BID x 5 days  
Atomoxetine 45 mg BID x 5 days  
Atomoxetine 60 mg BID x 5 days  
Atomoxetine 75 mg BID x 5 days  
Washout x 5 days

Twelve-lead EKGs were performed on treatment day 5 of each period, at 0, 1,2,4, and 12 hours after the morning dose. As Dr. Racoosin notes (page 3 of her memo), there were no dose related increases in the QTc interval in the EMs.

However, in the PMs, there was some evidence of a dose related increase in the QTc interval. Specifically, the change from baseline (placebo) for the 2 highest doses at the various time-points assessed was as follows:

Time	60 mg/kg/day	75 mg/kg/day
0	16.8	14.6
1	0.5	4.5
2	8	0.7
4	1	10.4
12	-3.3	8.9

As can be seen, at time 0 (just before the morning dose), significant increases in the QTc duration are seen. For the highest dose, it appears that there were also potentially important increases at 4 and 12 hours after dosing. Indeed, a relationship between plasma level and QTc increase was seen in PMs for the 0, 4, and 12 hour assessments. No patient met QTc outlier criteria, nor did any subject have a change from baseline of 60 msec.

If one examines the mean change in QTc from baseline for all of the time points (excluding Time 0), the following results are obtained:

30 m/k/d	45 m/k/d	60 m/k/d	75 m/k/d
-5.2	1.4	1.6	6.2

In an effort to further characterize the QTc prolongation, the sponsor performed Study LYAY, in which they administered fluoxetine (a potent CYP 2D6 inhibitor) together with atomoxetine to create phenotypic PMs. In this study, subjects were treated with the following regimen:

Fluoxetine 60 mg qd x 7 days, followed by  
 Fluoxetine 20 mg qd x 14 days, followed by  
 Atomoxetine 10 mg BID plus fluoxetine 20 mg qd x 5 days, followed by  
 Atomoxetine 45 mg BID plus fluoxetine 20 mg qd x 5 days, followed by  
 Atomoxetine 75 mg BID x 9 doses, followed by  
 Placebo, 1 dose and fluoxetine 20 mg qd.

Twelve-lead EKGs were obtained at days -2 and -1, and during treatment with fluoxetine and atomoxetine (on days 4 and 5 of each treatment period) and fluoxetine (on days 13 and 14 of the fluoxetine 20 mg qd period) at Time 0, 1, 2, 4, 8, and 12 after dosing.

Intervals were compared between no drug treatment and fluoxetine treatment to determine any prolongation associated with fluoxetine itself. Then, the differences between fluoxetine and fluoxetine with atomoxetine were calculated to determine the effect of the increased levels of atomoxetine on the QTc interval.

As can be seen in Dr. Boehm's review (page 68), there were no dose related increases in QTc intervals in this study. Similarly, no patient met QTc outlier criteria, and there were no systematic increases in QTc interval > 30 msec. There were no relationships between atomoxetine plasma levels and QTc duration.

As Dr. Boehm notes, however (page 67), the Cmax's of atomoxetine achieved by administering concomitant fluoxetine at the highest dose in this study were only about 70% of those seen in the natural PMs in Study LYAE (2784 and 4000, respectively), and the AUCs at the highest atomoxetine dose in this study were only about 62% of those seen in Study LYAE (23 and 37, respectively).

A third study, Study HFBJ, enrolled 16 EMs and 11 PMs in the following design:

Single daily doses of 10, 30, 60, 90, and 120 mg were administered, each separated by 4 days for EMs and 14 days for PMs. During this phase, each patient received placebo on day 1 (before any atomoxetine dose) and at one other day during the dose escalation. Following the single dose phase, EMs were randomized to atomoxetine 40 mg BID or placebo x 7 days; PMs received atomoxetine 40 mg BID x 7 days.

EKGs were performed at baseline, 2, and 24 hours after dosing.

In the single dose phase, there were no consistent changes in QTc in the EMs at either time point after dosing. In the PMs, the following changes in QTc were seen:

Dose	2 hours	24 hours
10 mg	0.5	-1.8
30 mg	6.5	1.6
60 mg	5.0	7.0
90 mg	7.9	6.8
120 mg	6.0	1.0

In the multi-dose phase, the changes (difference from placebo) in QTc were 5.5 and 7.9 msec in the EMs and PMs, respectively (for the PMs, their multi-dose data were compared to their own placebo data from the single dose phase).

A total of 5/16 EMs and 5/11 PMs had increases in the QTc of between 30 and 60 msec. There were no subjects who met outlier criteria.

The sponsor presented pooled single dose and pooled multiple dose data from the clinical pharmacology studies. The following differences between the 120 mg and placebo single doses in EMs and PMs were as follows:

Hour	EMs	PMs
1 hour	5.6	6.5
2 hours	2.4	7.2
4 hours	-1.5	7.8
12 hours	-2.3	4.8

The multiple dose pooled data largely reflects the results of Study LYAE, and, as pointed out by Dr. Boehm, therefore provide little new data.

In the controlled trials in pediatric patients, EKGs were monitored at multiple visits, but, as far as we know, not in any systematic temporal relationship to dosing. In these trials, the mean changes from baseline at endpoint in the drug and placebo groups were both negative, with the QTc on drug (-5.3 msec) more negative than on placebo (-4.4 msec). A slightly higher percentage of placebo patients met outlier criteria than did atomoxetine patients. No patients had an increase in QTc of greater than 60 msec, and none had a QTc of 500 msec or greater.

Dr. Boehm also examined the effects of metabolic status (EM vs PM) on QTc interval data from the controlled and open-label Phase 2/3 data.

There were no important differences in mean QTc duration between EMs and PMs overall, when considering change from baseline to endpoint. This was true also when limiting the analysis to patients whose maximum dose was at least 1.2 mg/kg/day.

Considering an outlier as a patient who had an increase in QTc duration of at least 30 msec and an absolute duration of at least 435 msec, there was a higher percentage of PMs (4.5%) compared to EMs (2.4%) who met these criteria, at a dose of at least 1.2 mg/kg/day (the numbers for any dose were essentially the same).

Also, a slightly greater percentage of PMs (3.7% at doses of at least 1.2 mg/kg/day) compared to EMs (1.4%) with normal baseline EKGs had a prolonged QTc interval (> 450 msec for males, >470 msec for females) at the maximum dose to which they were exposed using a database correction (the numbers using a Fredericia correction were 2.7% to 1%).

In the adult controlled trials, the ordering of results was the same as in the pediatric studies (slightly increased mean QTc on placebo compared to drug with

a slightly higher percentage of placebo patients with increases of 30 and 60 msec).

### Other Adverse Events

Drs Laughren and Racoosin summarize the other adverse events seen in patients treated with atomoxetine.

Important adverse events associated with atomoxetine use include dry mouth, insomnia, nausea, anorexia, constipation, decreased libido, dizziness, impotence, sweating, myalgia, dysuria, abnormal ejaculation, palpitations, dysmenorrhea, menstrual disorder, urinary retention, and impaired urination. As the reviewers point out, for a number of events, the incidence was greater in PMs than in EMs (see, for example, Dr. Racoosin's table on page 2). As Dr. Racoosin also notes, however, there was no increased incidence of discontinuations due to adverse events or serious adverse events in PMs compared to EMs (although, of course, the number of PMs, especially at therapeutic doses, was small).

As various of the reviewers have noted, a number of adverse events are worth special mention, including a slight increase in blood pressure and pulse (both slightly worse in PMs vs EMs), with an increase in orthostatic hypotension, also greater in PMs than in EMs, urinary outflow difficulties in adult men, sexual dysfunction, and, oddly, an increased incidence of appendicitis (a rate in pediatric patients about 2.5 that of the background rate). There were a number of cases of events called convulsions (a total of 6 in the database), but details were lacking; Dr. Boehm's review of 7/25/02 documents that none of these cases are unequivocally seizures, or drug related. There were no systematic important changes in laboratory values, with the possible exception of the changes seen in Alk Phos, as follows:

### Mean Change From Baseline

#### Pediatric Controlled Trials

Atomoxetine	-7.2
Placebo	9.2

#### All Pediatric Studies

Atomoxetine	-10.5
EMs	-10
PMs	-16.1

These findings are of potential interest, because of the effects on growth seen in the pediatric patients.

Specifically, in the pediatric controlled trials, there was a mean decrease in weight in the atomoxetine group of .38 kg, compared to a gain of 1.5 kg in the placebo treated patients. In these trials, the incidence of a loss of weight of at least 3.5% of body weight was 32% on drug, compared to 6% on placebo (for adults, the incidence of weight loss of at least 7% of body weight was 4.7% on drug, 0.4% on placebo). In the overall pediatric database (BID dosing), the incidence of a loss of at least 3.5% of body weight was 39%.

In Study LYAC, the fixed dose study, the following incidence of weight loss by dose was seen:

Dose	Change from Baseline	Percent with 3.5% Loss
Pbo	+1.7 kg	1.3%
0.5 m/k/d	+0.3 kg	7.1%
1.2 m/k/d	-0.4 kg	19.3%
1.8 m/k/d	-0.5 kg	29.1%

The sponsor did additional analyses to examine the long-term effects of treatment on weight gain. While pediatric patients treated for 1 and 1.5 years did gain weight (about 4 and 6.5 kg, respectively), they gained less than would be expected over this period of time; see Dr. Boehm's review, pages 54-55).

Regarding height, the mean increase in height in pediatric controlled trials was 0.89 cm for the atomoxetine treated patients and 1.14 cm for placebo patients.

In Study LYAC, placebo patients gained 1.8 cm, compared to 1.1, 1.0, and 1.0 cm for the low, mid, and high dose groups of atomoxetine, respectively. In the overall database, height increased, but not as much as expected.

In the overall database for pediatric patients who received doses of at least 1.2 mg/kg/day, PMs lost about 1.2 kg at endpoint compared to baseline, compared to a gain of about .77 kg in EMs. PMs gained about 1.5 cm in height, compared to a gain of about 2.2 cm in EMs (see the table in Dr. Boehm's review, page 53). Also, the incidence of weight loss of at least 3.5% of body weight in these patients was 64% for PMs and 45% for EMs.

## Comments

The sponsor has submitted the results of 6 randomized controlled trials that clearly establish the short-term effectiveness of atomoxetine in adults and pediatric patients with ADHD, given either once or twice a day. In addition, the sponsor has submitted safety data for over 2,300 subjects/patients that, in general, establish atomoxetine as safe for this population.

However, because atomoxetine is primarily metabolized by CYP2D6, a small percentage of patients (PMs, about 5-10% of Caucasians), will produce much higher plasma levels of the parent than other patients. In particular, PMs have, on average, about a 10 fold increase in the C<sub>ss</sub> avg compared to EMs for any given dose, and an AUC of between 7-10 fold and a C<sub>ss</sub> max of about 5 fold compared to EMs.

In general, the differences in plasma levels between EMs and PMs appear not to have resulted in important differences in adverse events; that is, there were no more serious ADRs seen in PMs compared to EMs (there were no deaths in the database). However, it is important to note that, although experience in 136 PMs was included in the application, only 13 PMs were exposed to a maximum daily dose equal to or greater than the therapeutic dose (1.2 mg/kg/d) for 6 months, and only 1 for a year (a total of 112 PMs were exposed to this dose overall). For this reason, it is difficult to assess the comparability of the serious ADR profile in the 2 metabolic strata, especially for ADRs associated with long-term treatment.

Atomoxetine use was associated with a number of ADRs (increased pulse and blood pressure, orthostatic hypotension, urinary outflow difficulties (in adult men), sexual dysfunction, and even a possible increase in appendicitis). However, of greatest concern is the possibility that atomoxetine increases the QTc interval.

The most serious signal for QTc prolongation arises from Study LYAE in which healthy adults (6 PMs and 10 EMs) were treated in succession with increasing doses of atomoxetine, up to 75 mg BID (the maximum effective dose is 60 mg BID). In the PMs, at 60 and 75 mg BID, the change from baseline was 16.8 msec and 14.6 msec, respectively, just before a morning dose at steady state (doses were given approximately 12 hours apart). In the 75 mg group, there were also increases of importance at 4 and 12 hours after dosing (10.4 and 8.9 msec). There was also a relationship between plasma levels and QTc duration in the PMs at Hours 0, 4, and 12.

Several other pieces of evidence also suggest that, in PMs, atomoxetine may increase the QT interval.

In a rising, single dose study in adults, the following QTc durations were noted:

Dose	2 hrs	24 hrs
10 mg	0.5	-1.8
30 mg	6.5	1.6
60 mg	5.0	7.0
90 mg	7.9	6.8
120 mg	6.0	1.0

Pooled single dose data from the clinical pharmacology studies revealed the following changes from placebo for the 120 mg dose:

	PM	EM
1 hour	6.5	5.6
2 hours	7.2	2.4
4 hours	7.8	-1.5
12 hours	4.8	-2.3

In the overall database, the proportion of PM patients who met outlier criteria (increase in QTc of at least 30 msec and an absolute QTc of 435 msec) was 4.5%, compared to 2.4% EMs. Further, 3.7% of PMs, compared to 1.2% of EMs, had a normal baseline QTc duration and a QTc duration of >450 msec in males and >470 msec in females at the endpoint.

While these data are suggest that atomoxetine may prolong the QTc interval, other evidence may suggest that there is no important effect.

In Study LYAE, the study designed to examine the QT effects of increasing dose, and in which the Hour 0 durations in the 60 and 75 mg dose groups provide the primary basis for the concern, it is important to note that, in the 60 mg group (Hour 0 QTc increase of 16.8 sec), the Hour 12 change is -3.3 msec. The Hour 12 time and the Hour 0 time both should represent C<sub>ss</sub> min. If we expect that there is a relationship between plasma level and QTc duration (however complicated that relationship may be), that relationship should be the same at similar plasma levels at similar times after dosing, at steady state. That seems not to be the case, at least for the 60 mg group. Even in the 75 mg group, the change in QTc duration is 14.6 msec at Hour 0, but 8.9 msec at Hour 12.

We typically expect the maximum increase in QT duration to correspond to T<sub>max</sub> (this assumption, of course, could be completely wrong; there could be a much more complicated relationship between plasma level and maximum QT duration). However, under this common assumption, again the 60 mg dose group appears not to be associated with a prolonged QT interval (the T<sub>max</sub> in PMs is about 2-4 hours; the 4 hour change in duration in the 60 mg group is 1 msec; although in the 75 mg group, it is 10.4 msec).

The sponsor performed an additional study, Study LYAY, in which they "created" phenotypic PMs by treating patients with atomoxetine and fluoxetine, a potent CYP2D6 inhibitor. In that study, there were no important changes in QTc duration. It should be pointed out, though, that patients in this study did not, in general, reach plasma levels of atomoxetine seen in the 60 or 75 mg groups in Study LYAE.

While there appeared to be an increase in QTc duration at 2 hours after single doses (from 30 mg to 120 mg) in Study HFBJ, it should be noted that 1) there were no real differences in degree of prolongation within this wide dose range, and 2) at steady state in this study, there was no meaningful difference between the change in QT duration between the EMs and PMs.

Even in the pooled single dose 120 mg data (in which increases in QT duration in PMs was seen), the EMs had an increase of 5.6 msec at 1 hour post-dose and 2.4 at 2 hours post-dose. If we consider Tmax in EMs to be about 1 hour, this analysis suggests that the increase at Tmax in EMs (5.6 msec) was about the same as the increase in QT duration at Tmax (2-4 hours) in PMs (about 7.5).

Importantly, in the entire database, analyses detected no systematic mean increase in QT duration in routinely collected EKGs, either in EMs or PMs, and even when considering patients who received at least the therapeutic dose. While it is true that these EKGs were not obtained in any systematic temporal relationship to dosing, it should be pointed out that the primary signal of concern arises out of EKGs measured at a single time point 12 hours after dosing (Hour 0; and then, as noted above, not consistently at a second time point 12 hours after dosing: Hour 12). If a drug prolongs the QT interval, but there is no predictable temporal relationship between maximum QT prolongation and maximum plasma level (which Study LYAE suggests), then we might expect that "randomly" measured EKGs would detect a QT prolonging effect. The clinical trial data did not detect such an effect.

Further, if there is little fluctuation in plasma levels during a dosing interval, we theoretically need not worry about the timing of the EKG during that interval; if the drug prolongs the QT, any EKG taken during the interval should detect it. With atomoxetine, the C<sub>ss</sub> min is about 50% of the C<sub>ss</sub> max; whether this represents minimal fluctuation or not (for these purposes) is not known. I do not believe that it is fruitful to speculate on the relationship between the shape of the plasma level-time concentration curve and QT prolongation in this case, other than to say that I believe that it is possible that atomoxetine could have a bona fide QT prolonging effect without such a simple, readily explainable relationship.

The question arises as to whether there are data examining the effects of atomoxetine on the QT interval appropriately timed to dose in the pediatric population. The sponsor contends that such data exist in 2 studies, LYBB and