CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
022516Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
EXCLUSIVITY SUMMARY

NDA # 022516 SUPPL # HFD # 170

Trade Name Cymbalta

Generic Name duloxetine hydrochloride

Applicant Name Eli Lilly and Company

Approval Date, If Known November 4, 2010

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy 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 a 505(b)(1), 505(b)(2) or efficacy supplement?  

      YES ☒ NO ☐

      If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

      505(b)(1), This is a type 6 NDA that will be rolled over into the parent NDA 021427 upon approval.

   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?

Three years

e) Has pediatric exclusivity been granted for this Active Moiety? YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade? YES ☒ NO ☐

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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 ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).
NDA#  21-427          Cymbalta
NDA#  21-733 (Type 6) Cymbalta
NDA#  22-148 (Type 6) Cymbalta

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 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.) IF “YES,” GO TO PART III.

PART III   THREE-YEAR EXCLUSIVITY FOR NDAs 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)
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.

   (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 8:

   (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 [ ]

Reference ID: 2859978
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:

**Studies:**
- HMGC
- HMEN
- HMEP
- HMFG
- HMEO

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 [x]

Investigation #2
- YES [ ]
- NO [x]

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

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

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"):

**Studies:**
- HMGC
- HMEN
- HMEP
- HMFG
- HMEO

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 #1-5

<table>
<thead>
<tr>
<th>IND # 63,615</th>
<th>YES ☒</th>
<th>NO ☐</th>
</tr>
</thead>
<tbody>
<tr>
<td>Explain:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Investigation #

<table>
<thead>
<tr>
<th>IND #</th>
<th>YES ☐</th>
<th>NO ☐</th>
</tr>
</thead>
<tbody>
<tr>
<td>Explain:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
(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 ☐ NO ☐

Explain:

Investigation #2

YES ☐ 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:

Name of person completing form: Ayanna Augustus, Ph.D.
Title: Regulatory Project Manager
Date: October 15, 2010

Name of Office/Division Director signing form: Bob Rappaport, M.D.
Title: Division Director, DAAP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AYANNA S AUGUSTUS
11/04/2010

BOB A RAPPAPORT
11/04/2010

Reference ID: 2859978
# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION¹

<table>
<thead>
<tr>
<th>NDA #</th>
<th>022516</th>
<th>NDA Supplement #</th>
<th>BLA STN #</th>
<th>If NDA, Efficacy Supplement Type:</th>
</tr>
</thead>
</table>

**Proprietary Name:** Cymbalta  
**Established/Proper Name:** duloxetine hydrochloride  
**Dosage Form:** capsules  
**RPM:** Ayanna Augustus  
**Division:** Division of Anesthesia and Analgesia Products

### NDAs:
- **NDA Application Type:** [ ] 505(b)(1) [ ] 505(b)(2)
- **Efficacy Supplement:** [ ] 505(b)(1) [ ] 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

### 505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
- **Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):**

Provide a brief explanation of how this product is different from the listed drug.

- If no listed drug, explain.
  - [ ] This application relies on literature.
  - [ ] This application relies on a final OTC monograph.
  - [ ] Other (explain)

### Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

**On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

- [ ] No changes  
- [ ] Updated  
  - Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

### Actions

- **Proposed action**
- **User Fee Goal Date is March 15, 2010**

- **Previous actions (specify type and date for each action taken)**

- **If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?**
  
  Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf)). If not submitted, explain.

  - [ ] Received

---

¹ The Application Information section is (only) a checklist. The Contents of Action Package section (beginning on page 5) lists the documents to be included in the Action Package.
## Application Characteristics

- **Review priority:**  
  - Standard [ ]  
  - Priority [ ]
- **Chemical classification (new NDAs only):** 6
- **Fast Track [ ]**  
  - Rx-to-OTC full switch [ ]
  - Rx-to-OTC partial switch [ ]
  - Direct-to-OTC [ ]
- **Rolling Review [ ]**
- **Orphan drug designation [ ]**

### NDAs: Subpart H
- **Accelerated approval (21 CFR 314.510) [ ]**
- **Restricted distribution (21 CFR 314.520) [ ]**

### BLAs: Subpart E
- **Accelerated approval (21 CFR 601.41) [ ]**
- **Restricted distribution (21 CFR 601.42) [ ]**

### Subpart I
- **Approval based on animal studies [ ]**

### Comments:
- Submitted in response to a PMR [ ]
- Submitted in response to a PMC [ ]
- Submitted in response to a Pediatric Written Request [ ]

### BLAs only: Ensure RMS-BLA Product Information Sheet for TBP and RMS-BLA Facility Information Sheet for TBP have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)
- Yes [ ]
- No [ ]

### BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)
- Yes [ ]
- No [ ]

### Public communications (approvals only)
- **Office of Executive Programs (OEP) liaison has been notified of action [ ]**
- **Press Office notified of action (by OEP) [ ]**
  - Yes [ ]
  - No [ ]
- **Indicate what types (if any) of information dissemination are anticipated [ ]**
  - None [ ]
  - HHS Press Release [ ]
  - FDA Talk Paper [ ]
  - CDER Q&As [ ]
  - Other [ ]

---

2 Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new RMS-BLA Product Information Sheet for TBP must be completed.

Version: 7/8/10
Reference ID: 2860745
## Exclusivity

- **Is approval of this application blocked by any type of exclusivity?**
  - No

- **NDAs and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)?**
  - Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.

- **(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application?**
  - (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)

- **(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application?**
  - (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)

- **(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application?**
  - (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)

- **NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)?**
  - (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)

## Patent Information (NDAs only)

- **Patent Information:**
  - Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.

- **Patent Certification [505(b)(2) applications]:**
  - Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.

- **[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).**

- **[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder).**
  - (If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).
[505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for each paragraph IV certification:

1. Have 45 days passed since the patent owner’s receipt of the applicant’s notice of certification?
   - Yes  
   - No
   (Note: The date that the patent owner received the applicant’s notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).
   
   If “Yes,” skip to question (4) below. If “No,” continue with question (2).

2. Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant’s notice of certification, as provided for by 21 CFR 314.107(f)(3)?
   - Yes
   - No
   
   If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.
   
   If “No,” continue with question (3).

3. Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?
   - Yes
   - No
   (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).
   
   If “No,” the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

4. Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?
   - Yes
   - No
   
   If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).
   
   If “No,” continue with question (5).
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner’s receipt of the applicant’s notice of certification?

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If “No,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If “Yes,” a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.

---

**CONTENTS OF ACTION PACKAGE**

- Copy of this Action Package Checklist\(^3\) November 4, 2010
- **Officer/Employee List**
  - List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)
  - Documentation of consent/non-consent by officers/employees
  - Included
- **Action Letters**
  - Copies of all action letters (including approval letter with final labeling) Action(s) and date(s)
  - Approval, November 4, 2010
- **Labeling**
  - Package Insert (write submission/communication date at upper right of first page of PI)
  - Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. October 14, 2010
  - Original applicant-proposed labeling May 15, 2009
  - Example of class labeling, if applicable

---

\(^3\) Fill in blanks with dates of reviews, letters, etc.
Version: 7/8/10
Reference ID: 2860745
- Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*

- Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.
- Original applicant-proposed labeling
- Example of class labeling, if applicable

- Labels *(full color carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*

- Proprietary Name
  - Acceptability/non-acceptability letter(s) *(indicate date(s))*
  - Review(s) *(indicate date(s))*

- Labeling reviews *(indicate dates of reviews and meetings)*

---

### Administrative / Regulatory Documents

- Administrative Reviews *(e.g., RPM Filing Review/Memo of Filing Meeting) *(indicate date of each review)*
- All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte
- NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*
- NDAs only: Exclusivity Summary *(signed by Division Director)*
- Application Integrity Policy (AIP) Status and Related Documents [http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm](http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm)
- Applicant is on the AIP
  - If yes, Center Director’s Exception for Review memo *(indicate date)*
  - If yes, OC clearance for approval *(indicate date of clearance communication)*

- Pediatrics *(approvals only)*
  - Date reviewed by PeRC February 17, 2010 and October 13, 2010
  - If PeRC review not necessary, explain: ______
  - Pediatric Record *(approvals only, must be reviewed by PERC before finalized)*

- Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*

- Outgoing communications *(letters (except action letters), emails, faxes, telecons)*

---

4 Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
<th>Dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal memoranda, telecons, etc.</td>
<td></td>
<td>10/13/10, 10/14/10, 10/15/10, 11/4/10</td>
</tr>
<tr>
<td>Minutes of Meetings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Regulatory Briefing (indicate date of mtg)</td>
<td>No mtg</td>
<td></td>
</tr>
<tr>
<td>- If not the first review cycle, any end-of-review meeting (indicate date of mtg)</td>
<td>N/A or no mtg</td>
<td></td>
</tr>
<tr>
<td>- Pre-NDA/BLA meeting (indicate date of mtg)</td>
<td>No mtg</td>
<td>November 16, 2007</td>
</tr>
<tr>
<td>- EOP2 meeting (indicate date of mtg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Other milestone meetings (e.g., EOP2a, CMC pilots) (indicate dates of mtgs)</td>
<td></td>
<td>Type C, March 31, 2006</td>
</tr>
<tr>
<td>Advisory Committee Meeting(s)</td>
<td>No AC meeting</td>
<td>August 19, 2010</td>
</tr>
<tr>
<td>- Date(s) of Meeting(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 48-hour alert or minutes, if available (do not include transcript)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decisional and Summary Memos</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office Director Decisional Memo (indicate date for each review)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Division Director Summary Review (indicate date for each review)</td>
<td>N/A or no mtg</td>
<td>November 4, 2010</td>
</tr>
<tr>
<td>Cross-Discipline Team Leader Review (indicate date for each review)</td>
<td>None</td>
<td>October 13, 2010</td>
</tr>
<tr>
<td>PMR/PMC Development Templates (indicate total number)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Clinical Information</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Reviews</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Clinical Team Leader Review(s) (indicate date for each review)</td>
<td>CDTL Memo October 13, 2010</td>
<td></td>
</tr>
<tr>
<td>- Clinical review(s) (indicate date for each review)</td>
<td>February 2, 2010</td>
<td></td>
</tr>
<tr>
<td>- Social scientist review(s) (if OTC drug) (indicate date for each review)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Financial Disclosure reviews(s) or location/date if addressed in another review OR</td>
<td>See clinical review</td>
<td></td>
</tr>
<tr>
<td>If no financial disclosure information was required, check here and include a review/memo explaining why not (indicate date of review/memo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)</td>
<td>Not applicable</td>
<td></td>
</tr>
<tr>
<td>Risk Management</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- REMS Documents and Supporting Statement (indicate date(s) of submission(s))</td>
<td></td>
<td>May 15, 2009</td>
</tr>
<tr>
<td>- REMS Memo(s) and letter(s) (indicate date(s))</td>
<td>None</td>
<td>OSE/DRISK February 19, 2009</td>
</tr>
<tr>
<td>- Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)</td>
<td>None requested 10/23/09, 1/22/10, 1/27/10, 2/18/10, 3/29/10</td>
<td></td>
</tr>
</tbody>
</table>

5 Filing reviews should be filed with the discipline reviews.
<table>
<thead>
<tr>
<th><strong>Clinical Microbiology</strong></th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Microbiology Team Leader Review(s) <em>(indicate date for each review)</em></td>
<td>☐ None</td>
</tr>
<tr>
<td>Clinical Microbiology Review(s) <em>(indicate date for each review)</em></td>
<td>☐ None</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Biostatistics</strong></th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statistical Division Director Review(s) <em>(indicate date for each review)</em></td>
<td>☒ None</td>
</tr>
<tr>
<td>Statistical Team Leader Review(s) <em>(indicate date for each review)</em></td>
<td>☐ None February 23, 2010</td>
</tr>
<tr>
<td>Statistical Review(s) <em>(indicate date for each review)</em></td>
<td>☐ None February 23, 2010</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Clinical Pharmacology</strong></th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Pharmacology Division Director Review(s) <em>(indicate date for each review)</em></td>
<td>☐ None</td>
</tr>
<tr>
<td>Clinical Pharmacology Team Leader Review(s) <em>(indicate date for each review)</em></td>
<td>☐ None</td>
</tr>
<tr>
<td>Clinical Pharmacology review(s) <em>(indicate date for each review)</em></td>
<td>☐ None</td>
</tr>
<tr>
<td>DSI Clinical Pharmacology Inspection Review Summary <em>(include copies of DSI letters)</em></td>
<td>☐ None</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Nonclinical</strong></th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacology/Toxicology Discipline Reviews</td>
<td></td>
</tr>
<tr>
<td>• ADP/T Review(s) <em>(indicate date for each review)</em></td>
<td>☐ None</td>
</tr>
<tr>
<td>• Supervisory Review(s) <em>(indicate date for each review)</em></td>
<td>☐ None</td>
</tr>
<tr>
<td>• Pharm/tox review(s), including referenced IND reviews <em>(indicate date for each review)</em></td>
<td>☐ None</td>
</tr>
<tr>
<td>Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <em>(indicate date for each review)</em></td>
<td>☐ None</td>
</tr>
<tr>
<td>Statistical review(s) of carcinogenicity studies <em>(indicate date for each review)</em></td>
<td>☐ No carc</td>
</tr>
<tr>
<td>ECAC/CAC report/memo of meeting</td>
<td>☐ None Included in P/T review, page</td>
</tr>
<tr>
<td>DSI Nonclinical Inspection Review Summary <em>(include copies of DSI letters)</em></td>
<td>☐ None requested</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Product Quality</strong></th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Quality Discipline Reviews</td>
<td></td>
</tr>
<tr>
<td>• ONDQA/OBP Division Director Review(s) <em>(indicate date for each review)</em></td>
<td>☒ None</td>
</tr>
<tr>
<td>• Branch Chief/Team Leader Review(s) <em>(indicate date for each review)</em></td>
<td>☐ None March 15, 2010</td>
</tr>
<tr>
<td>• Product quality review(s) including ONDQA biopharmaceutics reviews <em>(indicate date for each review)</em></td>
<td>☒ None</td>
</tr>
<tr>
<td>Microbiology Reviews</td>
<td>☒ Not needed</td>
</tr>
<tr>
<td>☐ NDAs: Microbiology reviews (sterility &amp; pyrogenicity) (OPS/NDMS) <em>(indicate date of each review)</em></td>
<td></td>
</tr>
<tr>
<td>☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <em>(indicate date of each review)</em></td>
<td></td>
</tr>
<tr>
<td>Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <em>(indicate date of each review)</em></td>
<td>☒ None</td>
</tr>
<tr>
<td>Environmental Assessment (check one) (original and supplemental applications)</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>☐ Categorical Exclusion <em>(indicate review date) (all original applications and all efficacy supplements that could increase the patient population)</em></td>
<td></td>
</tr>
<tr>
<td>☐ Review &amp; FONSI <em>(indicate date of review)</em></td>
<td></td>
</tr>
<tr>
<td>☑ Review &amp; Environmental Impact Statement <em>(indicate date of each review)</em> November 2, 2009</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Facilities Review/Inspection</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑ NDAs: Facilities inspections (include EER printout) <em>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites)</em></td>
</tr>
<tr>
<td>Date completed: March 15, 2010</td>
</tr>
<tr>
<td>☑ Acceptable</td>
</tr>
<tr>
<td>☐ Withhold recommendation</td>
</tr>
<tr>
<td>☐ Not applicable</td>
</tr>
<tr>
<td>☐ BLAs: TB-EER <em>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</em></td>
</tr>
<tr>
<td>Date completed:</td>
</tr>
<tr>
<td>☐ Acceptable</td>
</tr>
<tr>
<td>☐ Withhold recommendation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NDAs: Methods Validation <em>(check box only, do not include documents)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Completed</td>
</tr>
<tr>
<td>☐ Requested</td>
</tr>
<tr>
<td>☐ Not yet requested</td>
</tr>
<tr>
<td>☐ Not needed (per review)</td>
</tr>
</tbody>
</table>

---

6 I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.
Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

1. It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
2. Or it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
3. Or it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean any reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

1. The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
2. And no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
3. And all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

1. Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
2. Or the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
3. Or the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AYANNA S AUGUSTUS
11/05/2010

Reference ID: 2860745
Augustus, Ayanna

From: Jani, Parinda
Sent: Thursday, November 04, 2010 5:56 PM
To: 'Matt Kuntz'; Augustus, Ayanna
Subject: RE: Cymbalta

Thanks, we will be taking an action within a few minutes, so stay tuned.....

From: Matt Kuntz [mailto:KUNTZ_MATT@LILLY.COM]
Sent: Thursday, November 04, 2010 5:55 PM
To: Augustus, Ayanna; Jani, Parinda
Subject: RE: Cymbalta

Hello Parinda and Ayanna,
Thanks for the call! Per our discussion this afternoon, Lilly agrees to the following revision to the Highlights of Prescribing Information for Cymbalta:

------------------------INDICATIONS AND USAGE-------------------------------
Chronic Musculoskeletal Pain -(1.5).

If possible, could you send me a Word copy of the final, approved labeling?

Do you know if FDA intends to issue a press release? If so, do you think it will be this evening?

Thanks,
Matt

______________________________
Matt Kuntz, RPh, MBA, RAC
Global Regulatory Affairs - US
Eli Lilly and Company
Office 317.433.1766
Mobile 317.625.5151

CONFIDENTIALITY NOTICE: This e-mail message from Eli Lilly and Company (including all attachments) is for the sole use of the intended recipient(s) and may contain confidential and privileged information. Any unauthorized review, use, disclosure, copying, or distribution is strictly prohibited. If you are not the intended recipient, please contact the sender by reply e-mail and destroy all copies of the original message.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AYANNA S AUGUSTUS
11/05/2010
Hi Ayanna,

The Cymbalta (duloxetine hydrochloride) full waiver was reviewed by the PeRC PREA Subcommittee on October 13, 2010.

The Division recommended a full waiver because there are too few children with disease/condition to study.

The PeRC agreed with the Division to grant a full waiver for this product. The pediatric record is attached as proof of the PeRC’s review for Cymbalta.

Thank you.

George Greeley  
Regulatory Health Project Manager  
Pediatric and Maternal Health Staff  
FDA/CDER/OND  
10903 New Hampshire Avenue  
Bldg. 22, Room 6467  
Silver Spring, MD 20993-0002  
Phone: 301.796.4025  
Email: george.greeley@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AYANNA S AUGUSTUS
10/20/2010
Hi Matt,

Please send me a word copy of the last approved medication guide for cymbalta.

Thanks,
Ayanna

Ayanna Augustus, Ph.D.
Regulatory Project Manager
Division of Anesthesia and Analgesia Products
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22, Room 3219
10903 New Hampshire Ave
Silver Spring, MD 20993
301-796-3980 (phone)
301-796-9717 (fax)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AYANNA S AUGUSTUS
10/15/2010
Hi Matt,

Attached is the revised label for Cymbalta which has been reviewed by Dr. Rappaport. Please review and provide a label in clean and tracked changes. In addition, time has been set side on the Division calendar to discuss the labeling on Thursday, October 14th at 9 AM. Please confirm Lilly's availability for labeling discussion at that time and provide a call-in number as well.

Regards,
Ayanna

Hi Ayanna,

It looks as though container labels were included with an amendment dated 11 January 2010 (NDA 22-516 sequence # 0006). Please let me know if you don't find these or would like me to send them.

Any update regarding the pediatric waiver request or Dr. Rappaport's review of labeling?

Have a great weekend!
Many thanks,
Matt

Matt Kuntz, RPh, MBA, RAC
Global Regulatory Affairs - US
Eli Lilly and Company
Office 317.433.1766
Mobile 317.625.5151

CONFIDENTIALITY NOTICE: This e-mail message from Eli Lilly and Company (including all attachments) is for the sole use of the intended recipient(s) and may contain confidential and privileged information. Any unauthorized review, use, disclosure, copying, or distribution is strictly prohibited. If you are not the intended recipient, please contact the sender by reply e-mail and destroy all copies of the original message.
Hi Matt,

I noticed that the NDA submission does not contain a copy of the currently approved carton/container labels for Cymbalta nor was I able to find a reference to them. Please submit a copy of the labels to the NDA as soon as possible.

Regards,
Ayanna

Ayanna Augustus, Ph.D.
Regulatory Project Manager
Division of Anesthesia and Analgesia Products
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22, Room 3219
10903 New Hampshire Ave
Silver Spring, MD 20993
301-796-3980 (phone)
301-796-9717 (fax)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AYANNA S AUGUSTUS
10/15/2010
Hi Matt,

Obviously, a tcon with the stats group isn't going to happen today. The statistician has indicated that you should use the diary data in order to get the information for each week. There should be 12 graphs per study (one graph for each week).

If it will not be possible to provide the graphs by week based on BPI than provide graphs based on Diary measures.

Let me know if you have additional questions.

Ayanna
Hi Ayanna,

Our stats group is preparing a total of 10 graphs based on the three positive studies with BPI as primary:
3 for OA study HMFG - BPI collected at week 4,7,13
3 for CLBP study HMEN - BPI collected at week 4,7,13
4 for CLBP study HMGC - BPI collected at week 3,6,9,12

Please confirm this will satisfy the request or let me know if we need to modify the output. If we've interpreted the request correctly and no revisions are needed, we should be able to provide these by COB tomorrow.

Thanks,
Matt

Matt Kuntz, RPh, MBA, RAC
Global Regulatory Affairs - US
Eli Lilly and Company
Office 317.433.1766
Mobile 317.625.5151

CONFIDENTIALITY NOTICE: This e-mail message from Eli Lilly and Company (including all attachments) is for the sole use of the intended recipient(s) and may contain confidential and privileged information. Any unauthorized review, use, disclosure, copying, or distribution is strictly prohibited. If you are not the intended recipient, please contact the sender by reply e-mail and destroy all copies of the original message.

Hi Ayanna,

Thanks for the prompt reply. I've forwarded this to our stats group and will let you know if there are any additional questions.
Matt

Matt Kuntz/AM/LLY
09/22/2010 06:39 PM
To "Augustus, Ayanna" <Ayanna.Augustus@fda.hhs.gov>
cc Subject RE: NDA 22-516 Cymbalta - continuous responder graphs Link

CONFIDENTIALITY NOTICE: This e-mail message from Eli Lilly and Company (including all attachments) is for the sole use of the intended recipient(s) and may contain confidential and privileged information. Any unauthorized review, use, disclosure, copying, or distribution is strictly prohibited. If you are not the intended recipient, please contact the sender by reply e-mail and destroy all copies of the original message.
recipient, please contact the sender by reply e-mail and destroy all copies of the original message.

"Augustus, Ayanna" <Ayanna.Augustus@fda.hhs.gov>  

09/22/2010 05:26 PM  

To 'Matt Kuntz' <KUNTZ_MATT@LILLY.COM>  
cc 

Subject RE: NDA 22-516 Cymbalta - continuous responder graphs

Hi Matt,

I've populated the Division's responses to the questions below in red. If possible, please provide graphs by COB, Friday, September 24th.

Thanks,
Ayanna

From: Matt Kuntz [mailto:KUNTZ_MATT@LILLY.COM]  
Sent: Wednesday, September 22, 2010 4:12 PM  
To: Augustus, Ayanna  
Subject: RE: NDA 22-516 Cymbalta - continuous responder graphs

Hi Ayanna,
I've gotten the following three questions back from our Stats Group. Clarification on these points as soon as possible would be greatly appreciated.

1) Given that the request is for graphs by week, does the Agency want these graphs based on Diary measures or based on the in office BPI?  
Based on the in office BPI.

2) By continuous responder graphs, does the Agency want a table similar to those provided within the current draft labeling, but with a separate graph for each week?  
Yes, separate graphs for each week

3) For each of these responder graphs, should patients who drop out be considered nonresponders at every week after they drop out or should we count patients who drop out prior to study completion as nonresponders at all weeks, even those occurring prior to study drop out?  
The latter. All patients that drop out should be nonresponders at all weeks.

As much as we would like to, we may not be able to provide the graphs requested by noon tomorrow because of the underlying complexity and the need for validation of all the programs to ensure they are accurate. I'll keep you posted.

I'll send you the tcon info and Lilly attendees in a separate email.

Thanks
Matt

Matt Kuntz, RPh, MBA, RAC
Hi Matt,

Please provide continuous responder graphs for each week for CLBP and OA with the y-axis ranging from 1-100%. Please provide this data by noon, tomorrow or sooner if possible.

Also, please provide a call-in number for tomorrow's meeting and a list of Lilly attendees.

Thanks,
Ayanna

From: Matt Kuntz [mailto:KUNTZ_MATT@LILLY.COM]
Sent: Monday, September 20, 2010 9:44 AM
To: Augustus, Ayanna
Subject: RE: NDA 22-516 Cymbalta - next steps following the AC meeting

Hi Ayanna,
Do you think the review team will provide any comments back on our 9/13/10 proposed labeling prior to the teleconference this Thursday?

Could you provide the expected FDA participant names? I'll provide a teleconference number and Lilly participants later this week.

Thanks,
Matt

Matt Kuntz, RPh, MBA, RAC
Global Regulatory Affairs - US
Eli Lilly and Company
Office 317.433.1766
Mobile 317.625.5151
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AYANNA S AUGUSTUS
10/15/2010
Hi Ayanna,
Thanks for the call this morning. It was very helpful to confirm our understanding of review status.
Please don't hesitate to let me know if anything is needed from us.
Best,
Matt

Hi Matt,
We'll call in in about 10 minutes or so

Hi Ayanna,
While we don't have any specific labeling comments to discuss, we would be interested in understanding whether there are any remaining review items, and if not when an action is likely to occur. A very brief teleconference would be appreciated. Please let me know if we could still have a short tcon.
Thanks,

Matt Kuntz, RPh, MBA, RAC
Global Regulatory Affairs - US
Eli Lilly and Company
Office 317.433.1766
Mobile 317.625.5151

CONFIDENTIALITY NOTICE: This e-mail message from Eli Lilly and Company (including all attachments) is for the sole use of the intended recipient(s) and may contain confidential and privileged information. Any unauthorized review, use, disclosure, copying, or distribution is strictly prohibited. If you are not the intended recipient, please contact the sender by reply e-mail and destroy all copies of the original message.
Hi Matt,

Since there are only two minor revisions to the label I'm wondering if a tcon is still needed. Let me know if Lilly has any specific comments on the label that you'd like to discuss.

Thanks,
Ayanna

From: Matt Kuntz [mailto:KUNTZ_MATT@LILLY.COM]
Sent: Wednesday, October 13, 2010 5:09 PM
To: Augustus, Ayanna
Subject: RE: Cymbalta/container labels

Thanks Ayanna.

Please find attached the clean/track changes labeling.

We made two minor revisions (track changes version):
Line 1118: Studies in Chronic Pain Due to Osteoarthritis
Line 1066: Added a new sentence "Randomization was stratified by the patients' baseline NSAIDs-use status." prior to the existing sentence: "Subgroup analyses did not indicate that there were differences in treatment outcomes as a function of NSAIDs use." in order to inform why this subgroup data is being described. This suggested additional sentence comes from the OA section.

I look forward to speaking with you tomorrow morning.
Regards,
CONFIDENTIALITY NOTICE: This e-mail message from Eli Lilly and Company (including all attachments) is for the sole use of the intended recipient(s) and may contain confidential and privileged information. Any unauthorized review, use, disclosure, copying, or distribution is strictly prohibited. If you are not the intended recipient, please contact the sender by reply e-mail and destroy all copies of the original message.

"Augustus, Ayanna" <Ayanna.Augustus@fda.hhs.gov>

10/13/2010 03:12 PM
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AYANNA S AUGUSTUS
10/15/2010
Hi Matt,

The Division is going to need the revised pediatric plan/waiver request by **Friday 10:00 AM** rather than a week from today as discussed during this morning's teleconference. Lilly's revised plan/waiver request will need to be reviewed by the Pediatric Review Committee which, as you can imagine, will need to occur very soon.

Please let your team know that this will need to be formally submitted to the NDA by Friday morning.

Just to reiterate, if Lilly provides a revised plan, please be sure to provide dates for the following timeline:
- Final protocol submission date
- Study completion date
- Final study report submission date
- If Lilly requests a waiver, justification for the request. Let me know if you have any additional questions.

Thanks!!
Ayanna

Hi Ayanna.
I'm confirming for the teleconference tomorrow at 10:30 to discuss the pediatric plan.

Here is the call-in number for tomorrow.
Toll Free: 866-213-2145
International: 609-454-9913
Access Code: **4282830**

Lilly Participants:
- Vladimir Skljarevski, Medical Fellow, Cymbalta
- Smriti Iyengar, Sr. Research Scientist, Cymbalta
- Brady Cunningham, Senior Advisor - Project Management
There may be a couple other Lilly participants, but I have not been able to confirm their availability at this point.

Thanks,
Matt

Hi Ayanna.
I'll get back to you as soon as possible.
Thanks,
Matt

Hi Matt,

10/15/2010
In light of the revised indication of chronic musculoskeletal pain, the Division would like to schedule a brief teleconference for tomorrow, 9/28, at 10:30 AM to discuss the pediatric plan for this NDA. The pediatric plan will need to be revised to address the indication of chronic musculoskeletal pain.

Please confirm that 10:30 AM works for Lilly and provide a call-in number and list of attendees for this meeting.

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

/s/

AYANNA S AUGUSTUS
10/15/2010
Augustus, Ayanna

From: Augustus, Ayanna
Sent: Thursday, July 29, 2010 12:25 PM
To: 'Matt Kuntz'
Subject: RE: NDA 22-516 Cymbalta

Hi Matt,

Regarding the pediatric study for chronic pain, please provide the date by which the Division will receive the final study protocol, and the trial completion date by COB, Wednesday, August 4, 2010. Also, formally submit this to the NDA.

Thanks,
Ayanna

From: Matt Kuntz [mailto:KUNTZ_MATT@LILLY.COM]
Sent: Friday, July 23, 2010 12:13 PM
To: Augustus, Ayanna
Subject: RE: NDA 22-516 Cymbalta

Hi Ayanna,

I'm sorry for not getting a response back yesterday.

We'd prefer to wait until we've had an opportunity to review the FDA briefing document and make any adjustments to our core slides. This should help ensure the draft core presentation we send is reasonably stable. Based on a July 30th receipt, I think we can get our draft slides to you by Aug 9th, if not sooner.

Do you think this will provide enough time for the FDA presenters to react accordingly with their own slide development?

Best regards,
Matt

Matt Kuntz, RPh, MBA, RAC
Global Regulatory Affairs – US
Eli Lilly and Company
Office 317.433.1766
Mobile 317.625.5151

CONFIDENTIALITY NOTICE: This e-mail message from Eli Lilly and Company (including all attachments)
<table>
<thead>
<tr>
<th>Application Type/Number</th>
<th>Submission Type/Number</th>
<th>Submitter Name</th>
<th>Product Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA-22516</td>
<td>ORIG-1</td>
<td>ELI LILLY AND CO</td>
<td>CYMBALTA</td>
</tr>
</tbody>
</table>

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

/s/

AYANNA S AUGUSTUS
07/29/2010
Hi Bryan,

Our general practice is to provide the sponsor with the AC agenda which outlines the topics that will be discussed during the meeting. As was mentioned during the April 14th teleconference between the Division and Lilly, the Agency intends to present the safety and efficacy data in the NDA as well as the current data on the hepatotoxicity issue.

We also generally request that sponsors provide a copy of any draft presentations and a draft background package as this will help minimize overlap between the Agency and sponsor presentations so any draft copies you have to share at this time are appreciated.

The Division is still working on the meeting agenda so I don't have one to share at this time. Please keep in mind that the AC meeting date is tentative and not made official until the FR notice is published. Therefore, please do not issue any press releases about the meeting until the notice has been published.

Attached you will find a copy of the current draft label. Please note that there are several comments throughout the label that will need to be addressed, which I've also noted below:

1. Section 5.2, Revise the rate of ALT>3 times upper limit of normal for Cymbalta and placebo-treated patients to include the percentage of patients with both normal and abnormal baseline LFTs.
2. In section 6.1 Provide data to support the proposed changes to the exposure numbers for the placebo-controlled data for MDD and GAD as these numbers are inconsistent with the exposure numbers in the label approved on 11/19/09.
3. In section 6.2 in the DPNP section, provide an explanation for the new numbers.
4. In section 6.2 in the Chronic Low Back Pain section, include numbers from HMCG study.

Please provide a revised label in by COB, Friday, May 28th. Please accept all changes for which there is agreement between Lilly and the Division. Any changes that require additional discussion or review should be visible in track changes mode. Please email me if you have any questions.

Regards,
Ayanna
<table>
<thead>
<tr>
<th>Application Type/Number</th>
<th>Submission Type/Number</th>
<th>Submitter Name</th>
<th>Product Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA-22516</td>
<td>ORIG-1</td>
<td>ELI LILLY AND CO</td>
<td>CYMBALTA</td>
</tr>
</tbody>
</table>

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

/s/

AYANNA S AUGUSTUS
07/08/2010
Hi Ayanna,

The Cymbalta (duloxetine hydrochloride) partial waiver and deferral and plan was reviewed by the PeRC on February 17, 2010.

The Division recommended a partial waiver in patients 0-6 years because there are too few children with disease/condition to study and a deferral in patients 7-16 years of age because the product is ready for approval in adults.

The PeRC agreed with the Division to grant a partial waiver and deferral for this product.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
FDA/CDER/OND
10903 New Hampshire Avenue
Bldg. 22, Room 6467
Silver Spring, MD 20993-0002
Phone: 301.796.4025
Email: george.greeley@fda.hhs.gov

Please consider the environment before printing this e-mail.
<table>
<thead>
<tr>
<th>Application Type/Number</th>
<th>Submission Type/Number</th>
<th>Submitter Name</th>
<th>Product Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA-22516</td>
<td>ORIG-1</td>
<td>ELI LILLY AND CO</td>
<td>CYMBALTA</td>
</tr>
</tbody>
</table>

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

/s/

AYANNA S AUGUSTUS
06/29/2010
REQUEST FOR CONSULTATION

TO (Office/Division): OSE, Abolade Adeolu, RPM
FROM (Name, Office/Division, and Phone Number of Requestor): DAARP, Ayanna Augustus, RPM

DATE 6/7/10 IND NO. NDA NO. 22516 TYPE OF DOCUMENT Type 6 NDA DATE OF DOCUMENT 5/15/09

NAME OF DRUG Cymbalta (duloxetine hydrochloride) PRIORITY CONSIDERATION priority CLASSIFICATION OF DRUG analgesia DESIRED COMPLETION DATE 7/7/10

NAME OF FIRM: Eli Lilly and Co.

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL ☐ PROGRESS REPORT ☐ NEW CORRESPONDENCE ☐ DRUG ADVERTISING ☐ ADVERSE REACTION REPORT ☐ MANUFACTURING CHANGE / ADDITION ☐ MEETING PLANNED BY

☐ PRE-nda MEETING ☐ END-OF-PHASE 2a MEETING ☐ END-OF-PHASE 2 MEETING ☐ RESUBMISSION ☐ SAFETY / EFFICACY ☐ PAPER NDA ☐ CONTROL SUPPLEMENT

☐ RESPONSE TO DEFICIENCY LETTER ☐ FINAL PRINTED LABELING ☐ LABELING REVISION ☐ ORIGINAL NEW CORRESPONDENCE ☐ FORMATIVE REVIEW ☐ OTHER (SPECIFY BELOW): Summary review for Advisory Committee background package

II. BIOMETRICS

☐ PRIORITY P NDA REVIEW ☐ END-OF-PHASE 2 MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):

☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION ☐ BIOAVAILABILITY STUDIES ☐ PHASE 4 STUDIES ☐ DEFICIENCY LETTER RESPONSE ☐ PROTOCOL - BIOPHARMACEUTICS ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

☐ PHASE 4 SURVEILLANCE/EPIEDEMILOGY PROTOCOL ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below) ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY ☐ SUMMARY OF ADVERSE EXPERIENCE ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Cymbalta (duloxetine) is approved for the treatment of Major Depressive Disorder, Generalized Anxiety Disorder (NDA 21427-parent NDA in the Division of Psychiatry Products), Neuropathic pain and Fibromyalgia. NDA 22-516 for Cymbalta for the indication of treatment of chronic pain is being presented to the Anesthetic and Life Support Drugs Advisory Committee on August 19, 2010 to discuss the overall risk benefit of approving this medication for the broad indication of chronic pain. An important aspect of the discussion will be the safety profile of Cymbalta, specifically the associated hepatotoxicity. We request that you provide a summary document of the safety profile for duloxetine, including data regarding hepatotoxicity for the background package to be distributed to members of the advisory committee. Please submit the summary to Ayanna Augustus by July 7, 2010. Ellen Fields (6-1209) is the CDTL for this application.

Please contact Ayanna Augustus if you have any additional questions (6-3980)

SIGNATURE OF REQUESTOR Ayanna Augustus, RPM

METHOD OF DELIVERY (Check one)
☒ DARRTS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER
<table>
<thead>
<tr>
<th>Application Type/Number</th>
<th>Submission Type/Number</th>
<th>Submitter Name</th>
<th>Product Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA-22516</td>
<td>ORIG-1</td>
<td>ELI LILLY AND CO</td>
<td>CYMBALTA</td>
</tr>
</tbody>
</table>

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

/s/

AYANNA S AUGUSTUS
06/07/2010
**REQUEST FOR CONSULTATION**

**TO** (Office/Division): Division of Psychiatry Products, Paul David, CPMS; Steve Hardeman, CPMS

**FROM** (Name, Office/Division, and Phone Number of Requestor): DAARP, Ayanna Augustus, RPM

<table>
<thead>
<tr>
<th>DATE</th>
<th>IND NO.</th>
<th>NDA NO.</th>
<th>TYPE OF DOCUMENT</th>
<th>DATE OF DOCUMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/7/10</td>
<td></td>
<td>22516</td>
<td>Type 6 NDA</td>
<td>5/15/09</td>
</tr>
</tbody>
</table>

**NAME OF DRUG**

Cymbalta (duloxetine hydrochloride)

**PRIORITY CONSIDERATION**

priority

**CLASSIFICATION OF DRUG**

analgesia

**DESIRED COMPLETION DATE**

7/7/10

**NAME OF FIRM:** Eli Lilly and Co.

---

**REASON FOR REQUEST**

I. GENERAL

- NEW PROTOCOL
- PROGRESS REPORT
- NEW CORRESPONDENCE
- DRUG ADVERTISING
- ADVERSE REACTION REPORT
- MANUFACTURING CHANGE / ADDITION
- MEETING PLANNED BY

- PRE-ND A MEETING
- END-OF-PHASE 2a MEETING
- END-OF-PHASE 2 MEETING
- RESUBMISSION
- SAFETY / EFFICACY
- PAPER NDA
- CONTROL SUPPLEMENT

- RESPONSE TO DEFICIENCY LETTER
- FINAL PRINTED LABELING
- LABELING REVISION
- ORIGINAL NEW CORRESPONDENCE
- FORMATIVE REVIEW

- OTHER (SPECIFY BELOW): Summary review for Advisory Committee background package

II. BIOMETRICS

- PRIORITY P NDA REVIEW
- END-OF-PHASE 2 MEETING
- CONTROLLED STUDIES
- PROTOCOL REVIEW
- OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
- PHARMACOLOGY
- BIOPHARMACEUTICS
- OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
- BIOAVAILABILITY STUDIES
- PHASE 4 STUDIES

- DEFICIENCY LETTER RESPONSE
- PROTOCOL - BIOPHARMACEUTICS
- IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- PHASE 4 SURVEILLANCE/EPIEDEMIOLGY PROTOCOL
- DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
- COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- CLINICAL
- NONCLINICAL

**COMMENTS / SPECIAL INSTRUCTIONS:** NDA 22516 for Cymbalta (duloxetine) for the indication of treatment of chronic pain is being presented to the Anesthetic and Life Support Drugs Advisory Committee on August 19, 2010 to discuss the overall risk benefit of approving this medication for the broad indication of chronic pain. An important aspect of the discussion will be the safety profile of Cymbalta, specifically the associated hepatotoxicity. We request that you provide a summary document of the hepatotoxicity analysis performed by your division for the background package to be distributed to members of the advisory committee. Please submit the summary to Ayanna Augustus by July 7, 2010.

Please contact Ayanna Augustus if you have any additional questions (6-3980)

**SIGNATURE OF REQUESTOR**

Ayanna Augustus, RPM

**METHOD OF DELIVERY (Check one)**

☑ DARRTS ☐ EMAIL ☐ MAIL ☐ HAND

**PRINTED NAME AND SIGNATURE OF RECEIVER**

**PRINTED NAME AND SIGNATURE OF DELIVERER**
<table>
<thead>
<tr>
<th>Application Type/Number</th>
<th>Submission Type/Number</th>
<th>Submitter Name</th>
<th>Product Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA-22516</td>
<td>ORIG-1</td>
<td>ELI LILLY AND CO</td>
<td>CYMBALTA</td>
</tr>
</tbody>
</table>

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

/s/

AYANNA S AUGUSTUS
06/07/2010
**PART 1 - Requestor Information**

<table>
<thead>
<tr>
<th>Requestor's Name:</th>
<th>Ellen Fields</th>
<th>Today's Date:</th>
<th>2010-05-27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office/Division:</td>
<td>OND/DAAP</td>
<td>Desired Completion Date:</td>
<td>2010-08-02</td>
</tr>
<tr>
<td>Phone number:</td>
<td>301-796-1209</td>
<td>Drug name(s):</td>
<td>Cymbalta (duloxetine HCl)</td>
</tr>
<tr>
<td>Email Address:</td>
<td><a href="mailto:ellen.fields@fda.hhs.gov">ellen.fields@fda.hhs.gov</a></td>
<td>Drug Classification:</td>
<td>Antidepressant</td>
</tr>
</tbody>
</table>

**PART 2 - Purpose of Drug Use Data**

- AC Meeting/Sponsor Meeting
- Pediatric Drug Use Analysis (eg, BPCA, PdIT)
- Publication/Manuscript/Presentation/Research
- Safety Review
- Trade Name Review
- Other:

**PART 3 - Background and Reason for Request**

Background: We are currently reviewing NDA 22-516 for duloxetine for the treatment of chronic pain. An advisory committee meeting is planned for August 19, 2010 to discuss the risk/benefit of approving this drug for a larger patient population given its safety profile, specifically some liver toxicity. It is currently approved for the treatment of major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathy, and fibromyalgia (NDAs 21-427, 21-733, 22-148).

For comparison purposes, we need data regarding the use of cymbalta for both on and off label indications. We request drug use data by indication and also by type of prescriber, as well as overall prescribing data to present at the AC, so we can estimate how much, approving this drug for chronic pain, will actually increase the patient population. Please let me know if you have any questions.

**PART 4 - Specifics (time period of analysis, demographics such as age bands)**

- Duration of Use analysis*
- Concurrency analysis*
- Data to display gender breakdown
- Data to display age bands:
  - Age bands to include:

- Study Period:
  - Display Time from (Year): 2005 to (Year): 2010
  - monthly increments
  - yearly increments
  - Other: indications, prescribers

**PART 5 - CLEARANCE** (Required if data are to be shared outside of FDA or with non-FDA Persons)

Drug Use Data are proprietary and obtained by FDA under contract. Therefore, these data cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

CLEARANCE NEEDED?  | YES  | NO

For information on clearance procedures and forms, go to:
http://inside.fda.gov/CDER/OfficeofSurveillanceandEpidemiology/
<table>
<thead>
<tr>
<th>Application Type/Number</th>
<th>Submission Type/Number</th>
<th>Submitter Name</th>
<th>Product Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA-22516</td>
<td>ORIG-1</td>
<td>ELI LILLY AND CO</td>
<td>CYMBALTA</td>
</tr>
</tbody>
</table>

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

/s/

AYANNA S AUGUSTUS
06/03/2010
Hi Bryan,

The revised pediatric plan emailed on 1/15/10 was never formally sent via Gateway. Please try submitting it again.

In addition, please indicate the date Lilly plans to submit the final protocol for the pediatric study. Please provide a response by COB, Monday, February 8, 2010.

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

/s/

AYANNA S AUGUSTUS
02/10/2010
Hi Bryan,

The Agency is currently reviewing the REMS proposal for NDA 22516. Although Cymbalta has an approved Medication Guide, it does not have an approved REMS. Please submit to the parent NDA, 21427 the identical REMS proposal submitted to the chronic pain NDA.

In addition, please submit your latest version of Cymbalta labeling annotated with explanations for all changes in active links. Please submit this labeling by Monday, February 1st.

Regards,
Ayanna

Hi Ayanna,

I am sure you will let me know if there is anything else you need from Lilly for this NDA. After today's reviewers meeting, would you let me know if timelines have changed (specifically PMCs and labeling requests by February 22)? Thanks.

Kind regards,
Bryan
<table>
<thead>
<tr>
<th>Application Type/Number</th>
<th>Submission Type/Number</th>
<th>Submitter Name</th>
<th>Product Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA-22516</td>
<td>ORIG-1</td>
<td>ELI LILLY AND CO</td>
<td>CYMBALTA</td>
</tr>
</tbody>
</table>

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

/s/

AYANNA S AUGUSTUS
02/10/2010
Hi Ayanna,

The team met today and discussed the Division's proposed pediatric plan for chronic pain in children and adolescents. Lilly understands the need for pediatric data in chronic pain and are committed in providing an appropriate plan that would be able to implement within a reasonable time period. After careful preliminary consideration, we believe there are several pieces to the proposed plan below that will not be feasible in this population. We acknowledge the need to include children and will take that into consideration. We also understand the desire for a randomized, double-blind, placebo-controlled trial. We will also consider this within our updated plan.

We don't believe a study, such as proposed by the FDA below in CLBP is feasible within a reasonable timeframe based on the estimated children and adolescents with this condition. We will not be able to provide a proposal back by December 18, 2009 as requested and ask that the Division consider our revised pediatric chronic pain plan to be submitted no later than January 15, 2010. We realize the Division's internal review timelines and your January final review meeting, however, we want to provide to you a plan that is well researched and previewed both internally and externally on clinical need and feasibility. So we ask the Division to accept a response date to this request of on or before January 15, 2010.

Kind regards,
Bryan

Bryan Boggs, Pharm.D.
US Regulatory Affairs
Eli Lilly and Company
Office: 317-276-6685 FAX: 317-276-1652
Cell: 317-681-4997 bboggs@lilly.com

Dear Byran,

The clinical reviewer for this NDA has the following comments regarding the pediatric plan:

We have reviewed your proposed pediatric plan and found it unacceptable.
You are required to attempt to formulate an age appropriate formulation for younger patients if necessary. As part of the pediatric plan, you must submit the type(s) of studies you plan to carry out, along with the following dates: protocol submission, study start, study completion, and submission of final study report to the Agency.

Please submit the revised pediatric plan to the Agency by December 18, 2009.

Regards,
Ayanna

Ayanna Augustus, Ph.D.
Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Rheumatology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22, Rm 3219
10903 New Hampshire Ave
Silver Spring, MD 20993
301-796-3980 (phone)
301-796-9717 (fax)
<table>
<thead>
<tr>
<th>Application Type/Number</th>
<th>Submission Type/Number</th>
<th>Submitter Name</th>
<th>Product Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA-22516</td>
<td>ORIG-1</td>
<td>ELI LILLY AND CO</td>
<td>CYMBALTA</td>
</tr>
</tbody>
</table>

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

/s/

AYANNA S AUGUSTUS
12/18/2009
Hi Ayanna,

Attached is a response to your reviewers request on the FM discontinuation number change. I have also sent this as a formal response through eCTD to NDA 21-427. Please let me know if there are further questions.

Regards,

Bryan

Bryan Boggs, Pharm.D.
US Regulatory Affairs
Eli Lilly and Company
Office: 317-276-6685  FAX: 317-276-1652
Cell: 317-681-4997  bboggs@lilly.com

Confidentiality Notice - this e-mail message from Eli Lilly and Company (including all attachments) is for the sole use of the intended recipients(s) and may contain confidential and privileged information. Any unauthorized review, use, disclosure, copying or distribution is strictly prohibited. If you are not the intended recipient, please contact me by reply e-mail and destroy all copies of the original message.

Hi Bryan,

I hope you had a wonderful Thanksgiving holiday. Please indicate when the Division might receive a response to the information request sent to you on Monday, November 23rd (please see attachment).

Regards,

Ayanna
Hi Bryan,

Please send the outline of the background package as well as a copy of your slides on Dec 10th to me via email.

Regarding the updated labeling, please submit your revised labeling which should include the approved changes along with your proposed changes to address the chronic pain indication you are seeking. Please send updated labeling in tracked changes mode and a clean copy as WORD documents.

The Division is working with DPP on the review of the PAS submitted for Cymbalta (NDA 21427 SLR-033) which provides for changes to the fibromyalgia sections of the label. The clinical reviewer has the following comment and request for clarification:

In the prior approval supplement (PAS) submitted September 22, 2009, you request a change in the number of FM patients treated with duloxetine who discontinued treatment due to an adverse reaction and the accompanying percentage. Your rationale is that the number reflects what was listed in the Integrated Summary of Safety (Section 5.3.5.3) submitted with the initial application 22-148.

When we opened the initial application for NDA 22-148 (August 14, 2007), Table 2.7.4.6 from the ISS Tables, page 27 has the number for duloxetine patients who discontinued due to adverse event. Following revisions of the comments on the Case Report Forms, this number changed to (Table 2.7.4.7 from the ISS Tables, page 28).

Explain why is the number that reflects what was in the ISS submitted with the initial application 22-148."

Please provide a response by COB, Tuesday December 1, 2009

Regards,

Ayanna
04 December 2009

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products

RESPONSE TO FDA REQUEST FOR INFORMATION

Re: NDA 21-427; LY248686 Cymbalta® (Duloxetine Hydrochloride); eCTD Sequence No. 0081

Dear Dr. Laughren,

Reference is made to the Prior Approval Supplement submitted on 22 September 2009 to the Division of Psychiatry products (sequence 0072). Reference is also made to an FDA email sent to Bryan Boggs (Lilly) from Ayanna Augustus (FDA’s project manager for the Division of Anesthesia, Analgesia and Rheumatology Products) on 23 November 2009 requesting additional information. Lilly’s response to the Division’s information request is provided below. This response was also emailed separately to Ayanna Augustus.

FDA Request: “In the prior approval supplement (PAS) submitted September 22, 2009, you request a change in the number of FM patients treated with duloxetine who discontinued treatment due to an adverse reaction from [Redacted] and the accompanying percentage from [Redacted]. Your rationale is that the number reflects what was listed in the Integrated Summary of Safety (Section 5.3.5.3) submitted with the initial application 22-148.

When we opened the initial application for NDA 22-148 (August 14, 2007), Table 2.7.4.6 from the ISS Tables, page 27 has the number [Redacted] for duloxetine patients who discontinued due to adverse event. Following revisions of the comments on the Case Report Forms, this number changed to [Redacted] (Table 2.7.4.7 from the ISS Tables, page 28).

Explain why [Redacted] is the number that reflects what was in the ISS submitted with the initial application 22-148.”

Lilly Response: The rational stated in the original PAS submitted to FDA for Cymbalta (NDA 21427 SLR-033) for changing the number of FM patients treated with duloxetine who discontinued treatment due to an adverse reaction from [Redacted] contained an incorrect reference. The number of [Redacted] FM patients discontinued due to an adverse event is based upon table APP.5.2 in NDA 22-516 (page 4128, Section 5.3.5.3) instead of NDA 22-148.

The reason for the number change from [Redacted] in NDA 22-148 to [Redacted] in NDA 22-516 is due to the fact that a different database for study HMCJ was used for those 2 submissions. For NDA 22-148, data from an interim lock (for the acute, placebo-controlled study period only) was used, and patient HMCJ-112-2203 was recorded as discontinued due to “subject decision” in that interim database. Study HMCJ had an extension phase and final data locked occurred after the original FM submission (22-148). In the final database, the disposition reason for patient HMCJ-112-2203 was changed to “discontinued due to adverse events” (DCAE). For NDA 22-516, data from that HMCJ final lock was used, and this patient “HMCJ-112-2203” was added to the count of DCAE resulting [Redacted] patients discontinued due to adverse event from FM studies in NDA 22-516.
This submission is being sent via the FDA WebTrader Gateway. The submission was prepared on a virus protected workstation and all files were automatically scanned upon submission to the FDA. Lilly workstations are protected by the up-to-date version of the Symantec AntiVirus software. For eCTD technical questions concerning the format of the electronic submissions, please contact Amy Holloway at 317-276-9813 or holloway_amy_jo@lilly.com.

Please call me at (317) 276-6685 if you require further information or have any questions. Alternatively, you may contact Dr. Gregory T. Brophy, Senior Director, US Regulatory Affairs, at (317) 277-3799.

Sincerely,
ELI LILLY AND COMPANY

Bryan Boggs, Pharm.D.
Manager
U.S. Regulatory Affairs
<table>
<thead>
<tr>
<th>Application Type/Number</th>
<th>Submission Type/Number</th>
<th>Submitter Name</th>
<th>Product Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA-22516</td>
<td>ORIG-1</td>
<td>ELI LILLY AND CO</td>
<td>CYMBALTA</td>
</tr>
</tbody>
</table>

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

/s/

AYANNA S AUGUSTUS
12/18/2009
**REQUEST FOR DDMAC LABELING REVIEW CONSULTATION**

**Please send immediately following the Filing/Planning meeting**

TO: CDER-DDMAC-RPM

FROM: Ayanna Augustus, Project Manager, DAARP (6-3890)

<table>
<thead>
<tr>
<th>REQUEST DATE</th>
<th>IND NO.</th>
<th>NDA/BLA NO.</th>
<th>TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/25/08</td>
<td></td>
<td>22516</td>
<td><strong>NAME OF DRUG</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cymbalta</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>PRIORITY CONSIDERATION</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>standard</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>CLASSIFICATION OF DRUG</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Analgesic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>DESIRED COMPLETION DATE</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>January 18, 2010</td>
</tr>
</tbody>
</table>

**NAME OF FIRM:**

Eli Lilly and Company

PDUFA Date: March 15, 2010

**TYPE OF LABEL TO REVIEW**

- **TYPE OF LABELING:**
  - (Check all that apply)
  - PACKAGE INSERT (PI)
  - PATIENT PACKAGE INSERT (PPI)
  - CARTON/CONTAINER LABELING
  - MEDICATION GUIDE
  - INSTRUCTIONS FOR USE (IFU)

- **TYPE OF APPLICATION/SUBMISSION**
  - ORIGINAL NDA/BLA
  - IND
  - EFFICACY SUPPLEMENT / TYPE 6 NDA
  - SAFETY SUPPLEMENT
  - LABELING SUPPLEMENT
  - PLR CONVERSION

- **REASON FOR LABELING CONSULT**
  - INITIAL PROPOSED LABELING
  - LABELING REVISION

**EDR link to submission:** This product is approved for multiple indications in DPP and DAARP. The PI and Medication Guide contains new information to reflect the proposed chronic pain indication. Anjelina Pokrovichka is the clinical reviewer for this NDA. **\CDSESUB1\EVSPROD\NDA022516\022516.enx**

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

**COMMENTS/SPECIAL INSTRUCTIONS:**

- Mid-Cycle Meeting: October 15, 2009
- Labeling Meetings: January 5, 18, 27 and February 2
- Wrap-Up Meeting: January 15, 2010

**SIGNATURE OF REQUESTER**

**SIGNATURE OF RECEIVER**

**METHOD OF DELIVERY (Check one)**
- DAARTS
- HAND
<table>
<thead>
<tr>
<th>Application Type/Number</th>
<th>Submission Type/Number</th>
<th>Submitter Name</th>
<th>Product Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA-22516</td>
<td>ORIG-1</td>
<td>ELI LILLY AND CO</td>
<td>CYMBALTA</td>
</tr>
</tbody>
</table>

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

/s/

AYANNA S AUGUSTUS
11/25/2009
Hi Bryan,

The clinical reviewer has the following response to your proposes approaches to address our information requests:

1. For all the analyses requested, patients with abnormal baseline LFT's values should be defined as patients who had >1xULN liver function test values. Do not include patients with values <1xULN.

2. Markedly abnormal values for ALT and AST should be presented as >3xULN, >5xULN, and >10xULN.

3. For the extension phase of HMEN trial, in addition to the analysis that you are proposing, submit a separate analysis in which the 60mg and 120mg dose groups (regardless of what was their treatment assignment during the acute phase) are compared.

Regards,
Ayanna

Hi Ayanna,

Just to add additional clarity, I have added two sentences in blue from my previous message. Otherwise, this is the same as what I just sent to you.

Regards,
Bryan

Hi Ayanna,

We are currently working on providing the analyses requested in your e-mail from September 25. Our approach
to each of the requests are outlined below in RED. The Division’s original requests are in normal black text.

I am sending this to you so that the reviewers have a chance to comment on the expected analyses before we submit the results on October 7th. In the meantime, our team is working to provide a response as outlined below.

Kind regards,
Bryan

Bryan Boggs, Pharm.D.
US Regulatory Affairs
Eli Lilly and Company
Office: 317-276-6685  FAX:  317-276-1652
Cell:  317-681-4997   bboggs@lilly.com

Confidentiality Notice - this e-mail message from Eli Lilly and Company (including all attachments) is for the sole use of the intended recipients(s) and may contain confidential and privileged information. Any unauthorized review, use, disclosure, copying or distribution is strictly prohibited. if you are not the intended recipient, please contact me by reply e-mail and destroy all copies of the original message.

1. We request that you submit a separate pooled analysis (HMEO, HMEN, HMEP, and HMFG trials) of hepatic safety presented, by treatment group and duloxetine dose for the first 7 weeks and for the weeks 8 to 13, that includes only randomized subjects with abnormal baseline LFT’s values. Similar to the presentation approach in your August 14, 2009 submission, you can separate the hepatic-related analyses into four different sections:

- **Pooled analysis of hepatic-related adverse events.**

  **[Lilly Approach]** Patients with abnormal baseline LFT’s values will be defined as patients with abnormally high (>1X ULN) or low (<1X ULN) values for any of the hepatic labs including ALT, AST, Total Bilirubin, ALKPH and GGT at any time during baseline visits.

- **Pooled analysis of liver function tests, including mean change from baseline, shift analysis from baseline to abnormal (high and low), and markedly abnormal values.**

  **[Lilly Approach]** For the Mean change from baseline to endpoint/maximum, Lilly will create two separate tables: a) one for patients with abnormally high baseline values (i.e, the last nonmissing value at baseline is high); and b) one for patients with abnormally low baseline values (i.e, the last nonmissing value at baseline is low).

For the shift analysis from baseline to abnormal (either high or low), patients with abnormal high or low values at any baseline visits will be included in this analysis. Lilly will create the tables based on the mock up table below.

<table>
<thead>
<tr>
<th>Lab</th>
<th>Direction</th>
<th>Placebo N n %</th>
<th>DLX20QD N n %</th>
<th>DLX60QD N n %</th>
<th>DLX120QD N n %</th>
<th>DLX Total N n %</th>
</tr>
</thead>
<tbody>
<tr>
<td>XXX</td>
<td>Low-Lower</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low-Low</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low-Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low-High</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

10/1/2009
To assess "markedly abnormal values", Lilly will use two approaches: a) For ALT and AST, a definition commonly used for to assess a clinically significant high as >3XULN will be used, patients with abnormal high (>1XULN) values at any baseline visits will be included in this analysis. b) For all hepatic labs including ALT and AST, Lilly will also conduct treatment emergent potentially clinically significant (PCS) high analysis for all heptic labs, patients with abnormal high or low values at any baseline visits will be included in this analysis.

- Pooled analysis of discontinuation due to hepatic-related adverse event or elevations in LFTs.

[Lilly Approach] Patients with abnormal baseline LFT’s values will be defined as patients with abnormally high or low values for any of the hepatic labs including ALT, AST, Total Bilirubin, ALKPH and GGT at any time during baseline visits.

- Pooled analysis for laboratory values overtime for subjects with increase in ALT/AST and bilirubin values. Indicate whether treatment was discontinued or not and time of discontinuation related to obtaining lab tests.

[Lilly Approach] A previously submitted listing, "Table APP.2. Listing of Patients with Abnormal ALT, AST, or Bilirubin Values at Anytime During Postbaseline Visits" actually includes all patients with normal or abnormal baseline values. For this response, Lilly will create a report that is the same as Table APP.2, except that this new table will only include patients with abnormal high or low baseline values.

Below is the first page from Table APP.2 contained in the August 14, 2009 regulatory Response.

2. In addition, for the extension phase of the HMEN trial, submit the analyses described above presented by dose (duloxetine 60mg and duloxetine 120mg) at the time of the event. For these analyses, include both subjects who had normal and abnormal liver function tests at randomization.

[Lilly Approach] For all these analyses, Lilly will categorize patients into four dose groups: a) PLA_DLX60QD for patients who are on Placebo at acute phase and stayed on 60QD across the whole extension phase; b) PLA_DLX60/120QD for patients who are on Placebo at acute phase and titrated up to 120QD at any time during the extension phase; c) DLX_DLX60QD for patients who are on DLX at acute phase and stayed on 60QD across the whole extension phase; d) DLX_DLX60/120QD for patients who are on DLX at acute phase and started with 120QD or titrated up to 120QD at any time during the extension phase. In addition, PLA_DLX60QD and DLX_DLX60QD will be combined as DLX60QD group; PLA_DLX60/120QD and DLX_DLX60/120QD will also be combined as DLX60/120QD group.

Lilly believes this is the appropriate way to analyze the dose relationship due to the following reasons: a) Since dose titration is determined based on efficacy and safety considerations, direct comparison of
The clinical reviewer has the following information request.

The hepatic safety analysis submitted on August 14, 2009 included only subjects with normal baseline liver function tests (LFTs) values.

We request that you submit a separate pooled analysis (HMEO, HMEN, HMEP, and HMFG trials) of hepatic safety presented, by treatment group and duloxetine dose for the first 7 weeks and for the weeks 8 to 13, that includes only randomized subjects with abnormal baseline LFT’s values. Similar to the presentation approach in your August 14, 2009 submission, you can separate the hepatic-related analyses into four different sections:

- Pooled analysis of hepatic-related adverse events.
- Pooled analysis of liver function tests, including mean change from baseline, shift analysis from baseline to abnormal (high and low), and markedly abnormal values.
- Pooled analysis of discontinuations due to hepatic-related adverse event or elevations in LFTs.
- Pooled analysis for laboratory values overtime for subjects with increase in ALT/AST and bilirubin values. Indicate whether treatment was discontinued or not and time of discontinuation related to obtaining lab tests.

In addition, for the extension phase of the HMEN trial, submit the analyses described above presented by dose (duloxetine 60mg and duloxetine 120mg) at the time of the event. For these analyses, include both subjects who had normal and abnormal liver function tests at randomization.

Please provide a response by COB, Wednesday, October 7, 2009.

Regards,
Ayanna Augustus, Ph.D.
Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Rheumatology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22, Room 3219
10903 New Hampshire Ave
Silver Spring, MD 20993
301-796-3980 (phone)
301-796-9717 (fax)
<table>
<thead>
<tr>
<th>Application Type/Number</th>
<th>Submission Type/Number</th>
<th>Submitter Name</th>
<th>Product Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA-22516</td>
<td>ORIG-1</td>
<td>ELI LILLY AND CO</td>
<td>CYMBALTA</td>
</tr>
</tbody>
</table>

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

/s/

AYANNA S AUGUSTUS
10/01/2009
Hi Bryan,

The clinical reviewer has the following information request.

The hepatic safety analysis submitted on August 14, 2009 included only subjects with normal baseline liver function tests (LFTs) values.

We request that you submit a separate pooled analysis (HMEO, HMEN, HMEP, and HMFG trials) of hepatic safety presented, by treatment group and duloxetine dose for the first 7 weeks and for the weeks 8 to 13, that includes only randomized subjects with abnormal baseline LFT’s values. Similar to the presentation approach in your August 14, 2009 submission, you can separate the hepatic-related analyses into four different sections:

- Pooled analysis of hepatic-related adverse events.
- Pooled analysis of liver function tests, including mean change from baseline, shift analysis from baseline to abnormal (high and low), and markedly abnormal values.
- Pooled analysis of discontinuations due to hepatic-related adverse event or elevations in LFTs.
- Pooled analysis for laboratory values overtime for subjects with increase in ALT/AST and bilirubin values. Indicate whether treatment was discontinued or not and time of discontinuation related to obtaining lab tests.

In addition, for the extension phase of the HMEN trial, submit the analyses described above presented by dose (duloxetine 60mg and duloxetine 120mg) at the time of the event. For these analyses, include both subjects who had normal and abnormal liver function tests at randomization.

Please provide a response by COB, Wednesday, October 7, 2009.

Regards,
Ayanna

Ayanna Augustus, Ph.D.
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22, Room 3219
10903 New Hampshire Ave
Silver Spring, MD 20993
301-796-3980 (phone)
301-796-9717 (fax)
<table>
<thead>
<tr>
<th>Application Type/Number</th>
<th>Submission Type/Number</th>
<th>Submitter Name</th>
<th>Product Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA-22516</td>
<td>ORIG-1</td>
<td>ELI LILLY AND CO</td>
<td>CYMBALTA</td>
</tr>
</tbody>
</table>

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

/s/

AYANNA S AUGUSTUS
09/25/2009
Can you send this request to the sponsor please.

Yes
Ellen

Can we ask the sponsor the following:

“For trial HMEN, the discontinuation by dose analysis results, in particular discontinuations due to lack of efficacy during the last 6 weeks, presented in Table 2.7.4.21 (CSS, page 68) are different from the results from the same analysis submitted for NDA 22-333 (9/11/08 amendment, Tables 24 and 25, pp. 170-171).

Please explain.”
<table>
<thead>
<tr>
<th>Linked Applications</th>
<th>Submission Type/Number</th>
<th>Sponsor Name</th>
<th>Drug Name / Subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA 22516</td>
<td>ORIG 1</td>
<td>ELI LILLY AND CO</td>
<td>CYMBALTA</td>
</tr>
</tbody>
</table>

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

/s/

AYANNA S AUGUSTUS
07/30/2009
Hi Ayanna,
Can you please send the sponsor the question below.
Anjelina

Can we ask the sponsor the following question:

"The Financial Disclosure provided in Module 1 of the eCTD application (1.3.4), does not list the investigators for HMFG, similar to what you have for HMEN, HMEO and HMEP. Nevertheless, a financial disclosure form is included for (b) (4), sub investigator of Dr. Harvey Resnick for Study HMFG. The list description of the Investigators site for HMFG (Module 5, 5.3.5.1.7) does not include Dr. Harvey Resnick.

Please clarify."
<table>
<thead>
<tr>
<th>Linked Applications</th>
<th>Submission Type/Number</th>
<th>Sponsor Name</th>
<th>Drug Name / Subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA 22516</td>
<td>ORIG 1</td>
<td>ELI LILLY AND CO</td>
<td>CYMBALTA</td>
</tr>
</tbody>
</table>

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

/s/

AYANNA S AUGUSTUS
07/27/2009
Dear Dr. Boggs:

Please refer to your new drug application (NDA) dated May 15, 2009, received May 15, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Cymbalta (duloxetine hydrochloride), 20, 30, and 60 mg Capsules.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the user fee goal date is March 15, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by February 22, 2010.

During our filing review of your application, we identified the following potential review issues. Submit a response to these issues within 30 days of the date of this letter.

1. Submit revised exposure analysis for the primary chronic pain trials that describes drug exposure by duloxetine dose group (e.g. 20mg QD, 60mg QD, 120 mg QD, and any duloxetine dose). Present data in a table formatted as shown below and summarized in a text:
Table: Exposure to duloxetine by dose received – HMEN, HMEP, HMFG and HMEO

<table>
<thead>
<tr>
<th>Exposure duration (days)</th>
<th>DLX 20mg QD N=</th>
<th>DLX 60mg QD N=</th>
<th>DLX 120mg QD N=</th>
<th>Any DLX dose N=</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. For HMEN, HMFG, and HMEP trials, provide pooled analysis for subject disposition, presented by treatment group and duloxetine dose received (placebo, DLX 60mg QD, and DLX 120mg QD) for the first 7 weeks and for the weeks 8 to 13.

3. For the primary chronic pain analysis set (CP), including the HMEO, HMEN, HMEP, and HMFG trials, provide pooled analysis for adverse events (serious, events of interest, common and other significant adverse events) presented by treatment group and duloxetine dose received (i.e. placebo, duloxetine 20mg, duloxetine 60mg, and duloxetine 120mg) for the first 7 weeks and for the weeks 8 to 13. Data should be presented in tables and summarized in a text.

4. For the primary chronic pain analysis set (CP), including the HMEO, HMEN, HMEP, and HMFG trials, provide pooled analysis for laboratory data (chemistry, liver function, including analysis for AST, and hematology), vital signs, and ECG presented by treatment group (placebo, duloxetine 20mg, 60mg, and 120mg QD) for the first 7 weeks and the last 6 weeks of the treatment period. Include mean change from baseline, shift analysis from baseline to abnormal (high and low), markedly abnormal values and discontinuations due to abnormal laboratory, vital signs, and ECG parameters. Data should be presented in tables and summarized in a text.

5. Submit pooled analysis (HMEO, HMEN, HMEP, and HMFG trials) of hepatic safety presented by treatment group and duloxetine dose (placebo, duloxetine 20mg, 60mg, and 120mg QD) for the first 7 weeks and for the weeks 8 to 13. Include analysis of changes in aspartateaminotransferase (AST) values in this section. In order to assess reversibility of abnormal liver function overtime, in addition to the overall duloxetine exposure
integrated analyses set, provide available laboratory values over time for subjects with abnormal ALT/AST and bilirubin values for the primary chronic pain analysis set (CP). Indicate whether treatment was discontinued or not and time of discontinuation related to obtaining lab tests.

6. For HMEN and HMFG trials, conduct efficacy analysis for the comparison of duloxetine 60mg only dose versus placebo at Week 13, using BOCF and mBOCF imputation strategies and continuous responder analyses (BOCF).

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity, please consult the Division of Division of Anesthesia, Analgesia, and Rheumatology Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a full waiver of pediatric studies in patients with osteoarthritis for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

We acknowledge receipt of your request for a partial waiver of pediatric studies for ages birth to 7 years for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.
We acknowledge receipt of your request for a partial deferral of pediatric studies for ages 8 to 18 years for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, contact Ayanna Augustus, Regulatory Project Manager, at ayanna.augustus@fda.hhs.gov or (301) 796-3980.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

---------------------
Bob Rappaport
7/17/2009 04:21:33 PM
### REQUEST FOR CONSULTATION

**TO:** Raanan Bloom, OPS/PARS, (301)796-2185  
**FROM:** Don Henry, Project Manager, ONDQA, 301-796-4227 on behalf of Danae Christodoulou

**DATE**  
July 9, 2009

**IND NO.**  
NDA NO. 22-516  
**TYPE OF DOCUMENT**  
NDA submission  
**DATE OF DOCUMENT**  
May 15, 2009

**NAME OF DRUG**  
duloxetine HCl (Cymbalta)  
**PRIORITY CONSIDERATION**  
standard  
**CLASSIFICATION OF DRUG**  
analgesic (DAARP)  
**DESIRED COMPLETION DATE**  
October 31, 2009

**NAME OF FIRM:** Eli Lilly

### REASON FOR REQUEST

#### I. GENERAL

- NEW PROTOCOL
- PROGRESS REPORT
- NEW CORRESPONDENCE
- DRUG ADVERTISING
- ADVERSE REACTION REPORT
- MANUFACTURING CHANGE / ADDITION
- MEETING PLANNED BY
- PRE-NDA MEETING
- END-OF-PHASE 2a MEETING
- END-OF-PHASE 2 MEETING
- RESUBMISSION
- SAFETY / EFFICACY
- PAPER NDA
- CONTROL SUPPLEMENT
- RESPONSE TO DEFICIENCY LETTER
- FINAL PRINTED LABELING
- LABELING REVISION
- ORIGINAL NEW CORRESPONDENCE
- FORMULATIVE REVIEW
- OTHER (SPECIFY BELOW):

#### II. BIOMETRICS

- PRIORITY P NDA REVIEW
- END-OF-PHASE 2 MEETING
- CONTROLLED STUDIES
- PROTOCOL REVIEW
- OTHER (SPECIFY BELOW):
- CHEMISTRY REVIEW
- PHARMACOLOGY
- BIOPHARMACEUTICS
- OTHER (SPECIFY BELOW):

#### III. BIOPHARMACEUTICS

- DISSOLUTION
- BIOAVAILABILITY STUDIES
- PHASE 4 STUDIES
- DEFICIENCY LETTER RESPONSE
- PROTOCOL - BIOPHARMACEUTICS
- IN-VIVO WAIVER REQUEST

#### IV. DRUG SAFETY

- PHASE 4 SURVEILLANCE/EPIDEMILOGY PROTOCOL
- DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
- COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

#### V. SCIENTIFIC INVESTIGATIONS

- CLINICAL
- NONCLINICAL

### COMMENTS / SPECIAL INSTRUCTIONS:

A review of the environmental assessment is requested. This is an electronic submission (M1).

**SIGNATURE OF REQUESTOR**  
{See appended electronic signature page}

**METHOD OF DELIVERY (Check one)**

- DFS
- EMAIL
- MAIL
- HAND

**PRINTED NAME AND SIGNATURE OF RECEIVER**

**PRINTED NAME AND SIGNATURE OF DELIVERER**
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

---------------------
Ali Al-Hakim
7/10/2009 03:48:52 PM
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Office/Division): OSE/DRISK/Chris Wheeler, RPM  
FROM (Name, Office/Division, and Phone Number of Requestor): Division of Anesthesia, Analgesia, and Rheumatology Products/Ayanna Augustus, RPM

DATE 6/26/09
IND NO.  
NDA NO. 22-516
TYPE OF DOCUMENT New NDA
DATE OF DOCUMENT 5/15/09

NAME OF DRUG Cymbalta
PRIORITY CONSIDERATION Standard
CLASSIFICATION OF DRUG pain
DESIRED COMPLETION DATE 1/8/10

NAME OF FIRM: Eli Lilly & Co.

REASON FOR REQUEST

I. GENERAL

- NEW PROTOCOL
- PROGRESS REPORT
- NEW CORRESPONDENCE
- DRUG ADVERTISING
- ADVERSE REACTION REPORT
- MANUFACTURING CHANGE / ADDITION
- MEETING PLANNED BY
- PRE-NDA MEETING
- END-OF-PHASE 2a MEETING
- END-OF-PHASE 2 MEETING
- RESUBMISSION
- SAFETY / EFFICACY
- PAPER NDA
- CONTROL SUPPLEMENT
- RESPONSE TO DEFICIENCY LETTER
- FINAL PRINTED LABELING
- LABELING REVISION
- ORIGINAL NEW CORRESPONDENCE
- FORMULATIVE REVIEW
- OTHER (SPECIFY BELOW):

II. BIOMETRICS

- PRIORITY P NDA REVIEW
- END-OF-PHASE 2 MEETING
- CONTROLLED STUDIES
- PROTOCOL REVIEW
- OTHER (SPECIFY BELOW):
- CHEMISTRY REVIEW
- PHARMACOLOGY
- BIOPHARMACEUTICS
- OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
- BIOAVAILABILITY STUDIES
- PHASE 4 STUDIES
- DEFICIENCY LETTER RESPONSE
- PROTOCOL - BIOPHARMACEUTICS
- IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- PHASE 4 SURVEILLANCE/EPIEMIDOLOGY PROTOCOL
- DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
- COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- CLINICAL
- NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Please review and provide feedback on the sponsor's proposed REMS. The submission is located in the EDR \CDSESUB1\EVSPROD\NDA022516:0000. Anjelina Pokrovnichka is the clinical reviewer for this submission, Ellen Fields is the CDTL. Please contact Ayanna Augustus (6-3980) if you need additional information.

SIGNATURE OF REQUESTOR  
Ayanna Augustus

METHOD OF DELIVERY (Check one)
- DFS
- EMAIL
- MAIL
- HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
---------------------
Ayanna Augustus
6/26/2009 04:21:10 PM
Dear Dr Boggs:

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

Name of Drug Product: Cymbalta (LY248686, duloxetine hydrochloride)

Date of Application: May 15, 2009

Date of Receipt: May 15, 2009

Our Reference Number: 22-516

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 14, 2009 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.
The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/cder/ddms/binders.htm.

If you have any questions, call Tanya Clayton, Regulatory Project Manager, at (301) 796-0871.

Sincerely,

{See appended electronic signature page}

Tanya Clayton
Regulatory Health Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Tanya Clayton