CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-733

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

ITEM 14: PATENT CERTIFICATION

NDA 21-733
Cymbalta™ for Diabetic Neuropathic Pain
(duloxetine hydrochloride)

EXCLUSIVITY

Eli Lilly and Company (Lilly) claims a three year period of exclusivity for the use of duloxetine for the treatment of Diabetic Neuropathic Pain as provided by 21 C.F.R. 314.108(b)(5).

Clinical trials conducted which are essential to approval of this NDA are identified as follows:

F1J-MC-HMAW (acute phase) A Dose Response Study of Duloxetine Versus Placebo in Patients With Painful Diabetic Neuropathy Acute Therapy Phase

F1J-MC-HMAW (extension phase) A Dose Response Study of Duloxetine Versus Placebo in Patients With Painful Diabetic Neuropathy - Extension Phase

F1J-MC-HMAV(a): Duloxetine Versus Placebo in the Treatment of Patients with Painful Diabetic Neuropathy

F1J-MC-HMBT: An Open-Label Safety Study of Duloxetine in Patients with Painful Diabetic Neuropathy

As required by 21 C.F.R. 314.50(j)(4), Lilly certifies that to the best of Lilly's knowledge:

1. the above clinical investigation included in this application meets the definition of "new clinical investigation" as set forth in 21 C.F.R. 314.108(a);

2. the above clinical investigations are "essential to approval" of this application. Lilly, through its employees and others, electronically searched the Scientific literature via Medline, Derwent Drug File, SciSearch, Embase, PsychINFO, Biosis, and World Patent Index and has not discovered any published studies or publicly available reports for which Lilly is seeking approval. In Lilly's opinion and to the best of Lilly's knowledge, there are no published studies or publicly available reports to provide a sufficient basis for the approval of the conditions for which Lilly is seeking approval without reference to the new clinical investigations in this application.

3. the above clinical investigations were each conducted or sponsored by Lilly. Lilly was the sponsor named in the Form FDA-1571 of IND number 62,536 under which the new clinical investigation(s) that is essential to the approval of this application was conducted.

Feb 4, 2004

Gregory T. Brophy, PhD.
Director, US Regulatory Affairs

Date

ITEM 13: PATENT INFORMATION

NDA 21-733
Cymbalta™ for Diabetic Neuropathic Pain
(duloxetine hydrochloride)

The undersigned declares that the following patents cover the formulation, composition, and method of use of duloxetine, as indicated. This product is the subject of this application for which approval is being sought:

Patent Number	Patent Expiry Date	Type of Patent (Drug Substance, Drug Product, or Method of Use)
5,023,269	June 11, 2008	Drug Substance/Drug Product
5,508,276	July 18, 2014	Drug Product

The above patents are all owned by or exclusively licensed by Eli Lilly and Company, Indianapolis, IN

Gregory T. Brophy, Ph.D.
Director, US Regulatory Affairs

Feb 4, 2004
Date

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER
21-733

NAME OF APPLICANT / NDA HOLDER
Eli Lilly and Company

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Cymbalta™

ACTIVE INGREDIENT(S)	STRENGTH(S)
Duloxetine Hydrochloride	20mg, 30mg, — 60mg

DOSAGE FORM
Capsules delayed release pellets, oral

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,023,269	6/11/1991	6/11/2008

d. Name of Patent Owner
Eli Lilly and Company

Address *(of Patent Owner)*
P.O. Box 6288

City/State
Indianapolis, IN

ZIP Code	FAX Number *(if available)*
46206-6288	317-276-3861
Telephone Number	**E-Mail Address *(if available)***
317-276-2958	patents@lilly.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

General Patent Counsel.
Eli Lilly and Company

Address *(of agent or representative named in 1 e.)*
P.O. Box 6288

City/State
Indianapolis, IN

ZIP Code	FAX Number *(if available)*
46206-6288	317-276-3861
Telephone Number	**E-Mail Address *(if available)***
317-276-2958	patents@lilly.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☐ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No

4.2	Patent Claim Number *(as listed in the patent)* 20	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* A method for inhibiting serotonin reuptake	

4.2	Patent Claim Number *(as listed in the patent)* 24	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* A method for inhibiting norepinephrine reuptake	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below.)*

Date Signed: 1/21/04

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

- ☐ NDA Applicant/Holder
- ☐ NDA Applicant s/Holder's Attorney, Agent (Representative) or other Authorized Official
- ☐ Patent Owner
- ☒ Patent Owner s Attorney, Agent (Representative) or Other Authorized Official

Name
Arvie J. Anderson

Address	City/State
P.O. Box 6288	Indianapolis, IN
ZIP Code	**Telephone Number**
46206-6288	317-277-7217
FAX Number *(if available)*	**E-Mail Address *(if available)***
317-276-3861	patents@hlly.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- **Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.**
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER
21-733

NAME OF APPLICANT / NDA HOLDER
Eli Lilly and Company

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Cymbalta™

ACTIVE INGREDIENT(S)
Duloxetine Hydrochloride

STRENGTH(S)
20mg, 30mg, — 60mg

DOSAGE FORM
Capsules delayed release pellets, oral

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii), with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,508,276	4/16/1996	7/18/2014

d. Name of Patent Owner

Eli Lilly and Company
Shionogi & Co.

Address *(of Patent Owner)*
P.O. Box 6288

City/State
Indianapolis, IN

ZIP Code
46206-6288

FAX Number *(if available)*
317-276-3861

Telephone Number
317-276-2958

E-Mail Address *(if available)*
patents@lilly.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

☞

General Patent Counsel,
Eli Lilly and Company

Address *(of agent or representative named in 1.e.)*
P.O. Box 6288

City/State
Indianapolis, IN

ZIP Code
46206-6288

FAX Number *(if available)*
317-276-3861

Telephone Number
317-276-2958

E-Mail Address *(if available)*
patents@lilly.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes ☐ No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes	

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)	Date Signed
Arvie J. Anderson	1/21/04

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name: Arvie J. Anderson	
Address: P.O. Box 6288	City/State: Indianapolis, IN
ZIP Code: 46206-6288	Telephone Number: 317-277-7217
FAX Number *(if available)*: 317-276-3861	E-Mail Address *(if available)*: patents@lilly.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make *any other patented change regarding the drug, drug* product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman *patent extension already granted. Do not include* any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXCLUSIVITY SUMMARY FOR NDA # 21-733__ SUPPL #_____

Trade Name Cymbalta___ Generic Name duloxetine hydrochloride

Applicant Name _Eli Lilly & Co. HFD # 170_____

Approval Date If Known _September 3, 2004__

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 question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_X_/ NO /___/

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

__505(b)(1)_____

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 /_X_/ 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 /_X_/ NO /___/

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

___3 years_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen 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 /_X_/

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 /_X_/ NO /___/

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

NDA# ___21-427_
Cymbalta (duloxetine hydrochloride)Delayed-release Capsules

NDA# _____ _____

NDA# _____ _____

2. Combination product.

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

YES /___/ NO /_X_/

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 NDA'S AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations"

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

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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 /X_/ 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 /_X_/

(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 /_X_/

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 /_X_/

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:

_____HMAVa_____

_____HMAW_____

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_/

Investigation #2 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"):

_HMAVa_____ _____

_HMAW_____ _____

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

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

Investigation #1

IND # 62,536_ YES /X__/ NO /___/ Explain: _____

Investigation #2

IND # 62536_ YES /_X_/ NO /___/ Explain: _____

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

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

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

YES /___/ NO /_X_/

If yes, explain: _____

{See appended electronic signature page}

Lisa Marie Malandro
Regulatory Project Manager

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Division Director
Division of Anesthetic, Critical Care
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Form OGD-011347 Revised 05/10/2004

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/s/

Bob Rappaport
9/3/04 06:28:22 PM

DEBARMENT CERTIFICATION

NDA Application No.: 21-733

Drug Name: Duloxetine Hydrochloride

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Gregory T. Brophy, Ph.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By: _____
for Gregory T. Brophy, Ph.D.

Title: Director, U.S. Regulatory Affairs

March 02, 2004

PEDIATRIC PAGE

NDA # : 20-733 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: March 3, 2004 **Action Date:** September 3, 2004

HFD 170 **Trade and generic names/dosage form:** Cymbalta (duloxetine hydrochloride) Delayed-release Capsules

Applicant: Eli Lilly & Company **Therapeutic Class:** 6P/2040100

Indication previously approved: Major Depressive Disorder

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

Number of indications for this application: 1

Indication #1: management of neuropathic pain associated with diabetic peripheral neuropathy

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

X **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____ **kg**____ **mo.**____ **yr.**____ **Tanner Stage**____
Max____ **kg**____ **mo.**____ **yr.**____ **Tanner Stage**____

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

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

Other:_____

Date studies are due (mm/dd/yy): _____

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

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

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

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: **NDA 21-733**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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/s/

Lisa Malandro
9/3/04 06:28:22 PM

Malandro, Lisa

From: Sharon L Hoog [HOOG_SHARON_L@LILLY.COM]
Sent: Friday, September 03, 2004 5:41 PM
To: MALANDROL@CDER.FDA.GOV
Cc: Sharon L Hoog; Jole O Rodriguez; Lisa A Vierhile; Gregory T Brophy
Subject: NDA 21-733: Follow-up regarding teleconference 3 Sep 04

Hello Lisa,

This note to file is to record Lilly's understanding of the agreement reached today during a teleconference between Lilly and HFD-170 personnel, regarding the naming of duloxetine, (Item 1 of the Note to Reviewer sent to FDA at approximately 12;45 EST).

FDA stated that the recommendation for nomenclature for duloxetine was based on an FDA Guidance, and therefore Lilly is required to conform to that Guidance and implement the changes as requested. FDA acknowledged a prior agreement between Lilly and two other review divisions at FDA that a different naming convention could be used, and therefore is in agreement that the changes may be made at the next printing opportunity.

Lilly agreed to make the recommended changes at the next printing opportunity for Cymbalta, and will use current printed material until it is exhausted.

Thanks very much,

Sharon

Sharon L. Hoog, M.D.
Advisor
U.S. Regulatory Affairs
317-276-5220

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/s/

Lisa Malandro
9/3/04 06:20:53 PM
CSO

Malandro, Lisa

From: Malandro, Lisa

Sent: Tuesday, August 24, 2004 3:43 PM

To: 'Sharon L Hoog'

Subject: NDA 21-733 Duloxetine Information Request

Sharon,
Please see the attached information request. Response to this request should be made as an electronic amendment to the NDA as soon as possible. In the interest of time, you may email me a copy of the response.
If you have any questions, please do not hesitate to contact me.
Thanks,
Lisa

APPEARS THIS WAY
ON ORIGINAL

Aug 24, 2004

1. Please provide dose-by-duration tables for the 'secondary safety database' similar to your Table ISS.6.4.1

   If possible, provide three separate dose-by-duration tabulations for the non-DPN studies/exposures
   - Controlled trials
   - Uncontrolled trials
   - All trials

For the following requests (#2, #3, #4) use the same baseline observation carried forward method for imputation of missing efficacy data as in our previous request:

For each patient that did not complete the acute treatment phase, that patient's '24-hour average pain score' at endpoint (or the timepoint being evaluated) should be equal to their '24 hour average' baseline pain score. The 24-hour average pain score at 'endpoint' should not be calculated based upon their last available 24-hour average pain scores.

For both studies HMAW and HMAVa

2. Determine (and tabulate, by dose) for all 'sustained responders' at week 12,
   - the first week that 'clinical response' was achieved (time to clinical response), and
   - the first week that 'sustained response' was achieved (time to sustained response)

3. Provide analyses of '24-hour average pain score' change from baseline-to-endpoint (using BOCF), as presented in Tables HMAW.11.8 and HMAVa.11.9, with least squares means for change from baseline, and pairwise comparisons.

4. For Figures 1, 2 and 3, from your 7/20/04 response (labeled "threshold plot of the 24-hour average pain score ...with noncompleters excluded from the numerator")
   Reverse the X-axes so that it begins at zero and goes up to 100 (instead of 100 to 0 as they are now)

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/s/

Lisa Malandro
8/24/04 05:35:43 PM

4 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Eugene Richard Blonsky, M.D.
Pain and Rehabilitation Clinic of Chicago
640 N. LaSalle, Suite 610
Chicago, Illinois 60610

AUG 18 2004

Dear Dr. Blonsky:

Between July 7 and 20, 2004, Mr. Bruce H. McCullough, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol # F1J-MC-HMAV entitled: "Duloxetine Versus Placebo in the Treatment of Patients with Painful Diabetic Neuropathy") of the investigational drug Cymbalta (duloxetine hydrochloride), performed for Eli Lilly and Company. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, Mr. McCullough presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You did not conduct an investigation in accordance with the investigational plan (21 CFR 312.60).

   The protocol required subjects taking beta-blockers to have been taking them for a minimum of three months prior to enrollment. Subject #401 started taking Toprol-XL, a beta-blocker, in October of 2002, and was enrolled in the study on December 2, 2002.

2. You did not maintain accurate case histories with respect to observations and data pertinent to the investigation (21 CFR 312.62[b]).

   For subject #401, there was a discrepancy between the case report form and the Adverse-Events Running Log for the reporting of the adverse event of decreased appetite on 2/22/03. Both the case report form and the Adverse-Events Running Log asked if the event was possibly related to the study drug. The box was marked "yes" on the case report form and "no" on the Adverse-Events Running Log.

We acknowledge the corrections you have made in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies

We appreciate the cooperation shown Investigator McCullough during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Joseph P. Salewski

Joseph P. Salewski.
Acting Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

CFN/FEI: 3004612949
Field Classification: VAI
Headquarters Classification:
_____1)NAI
_X__2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

If Headquarters classification is a different classification, explain why:

Deficiencies noted:
__X__failure to adhere to protocol (05)
__X__inadequate and inaccurate records (06)

cc:
HFA-224
HFD-170 Doc.Rm. NDA# 21-733
HFD-170 Review Div.Dir. (Rappaport)
HFD-170 MO (Josefberg)
HFD-170 PM (Malandro)
HFD-46/47c/r/s/ GCP File # 11256
HFD-46/47 GCP Reviewer (Currier)
HFR-CE650 DIB (Berg)
HFR-CE6250 Bimo Monitor (Yuscius)
HFR-CE650 Field Investigator (McCullough)
GCF-1 Seth Ray

r/d: CAC: 8/6/04
reviewed:JLS:
f/t:CAC:

o:\cac\2004\blonsky.N21733.LTR.doc

Reviewer Note to Rev. Div. M.O.

The inspection of Dr. Blonsky was one of two routine PDUFA assignments issued to verify data for NDA 21-733. The inspection covered protocol F1J-MC-HMAV. At this site, 19 subjects were screened for the acute treatment phase 2; 14 completed phase 2 and were allowed to continue to the extension, open-label phase. Records for all 19 screened subjects were evaluated during the inspection. At the time of this inspection, 6 subjects had completed the extension phase, 4 were lost to follow-up and 4 more were expected to complete in a few months.

Two minor problems were found during the inspection. One subject had not been taking a beta blocker for a full 3 months prior to enrollment (as was required by the protocol). He had been

taking Toprol – XL for 2 months but was inadvertently enrolled. When the site discovered the protocol violation, they contacted the sponsor who told them to continue the subject (who was then in the extension phase). There were no reported AEs or safety issues that developed from this protocol violation.

The second problem was with the reporting of an adverse event for the same subject. One episode of decreased appetite was reported as study-drug related on the case report form, but the supporting source document, the Adverse-Events Running Log, indicated the AE was not study-drug related. The site claims the CRF data is correct. Unfortunately, the line listing of AEs we got from the sponsor to send as background material for the inspection, shows the AE as NOT study-drug related. Either the site changed the data on the CRF and neglected to tell the sponsor or the sponsor changed the data. Either way, the error is not clinically significant. This was one of approximately 350 AEs reported for that study site. All other AEs were accurately reported on CRFs and were accurately represented in the line listings.

Neither problem mentioned above would appear to jeopardize the validity of the study results. The data from this study can be used to support an approval decision for the NDA.

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/s/

Joseph Salewski
8/24/04 03:17:00 PM

Memorandum

To: NDA 21-733

From: R. Daniel Mellon, Ph.D., Pharmacology Toxicology Supervisor,
Division of Anesthetic, Critical Care and Addiction Drug Products

Date: August 13, 2004

Re: Duloxetine NDA Pharmacology Toxicology Review

Cymbalta® (duloxetine hydrochloride)

Indication: Pain due to Diabetic Peripheral Neuropathy (DPN)

Eli Lilly and Company submitted NDA 21-733 (Duloxetine for the , on March 3, 2004. This is the third indication to receive an NDA for this drug product; therefore, the Pharmacology Toxicology Data have already been scrutinized by two Divisions. Following several review cycles, Duloxetine was just recently approved by the Division of Neuropharmacologic Drug Products (NDA 21-427 for depression) and for stress urinary incontinence).

Dr. Linda Fossom in the Division of Neuropharmacologic Drug Products completed the first full NDA review of the Pharmacology and Toxicology data on this drug. Dr. Laurie McLeod-Flynn (HFD-580) re-examined the liver data due to clinical suggestions of potential liver toxicity in the drug treatment group (the NDA in HFD-580) was originally deemed approvable and has been resubmitted by the sponsor.

Dr. Suzanne Thornton-Jones was the primary pharmacology/toxicology reviewer of the NDA in DACCADP as well as the IND (62,536). **I concur with Dr. Thornton-Jones' conclusions and recommendations that NDA 21-733 is approvable from the pharmacology and toxicology perspective.**

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/s/

R. Daniel Mellon
8/13/04 11:11:33 AM
PHARMACOLOGIST

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA 21-733

Trade Name: Cymbalta (duloxetine hydrochloride)
Generic Name:
Strengths: 20/30 —,60 mg

Applicant: Eli Lilly and Company

Date of Application: March 2, 2004
Date of Receipt: March 3, 2004
Date clock started after UN: NA
Date of Filing Meeting: April 19, 2004
Filing Date: May 1, 2004
Action Goal Date (optional): User Fee Goal Date: September 3, 2004

Indication requested: —

Type of Original NDA: (b)(1) ___X_____ (b)(2) _____
OR
Type of Supplement: (b)(1) _____ (b)(2) _____

Therapeutic Classification: S _____ P ____1_____
Resubmission after withdrawal? ___NA_____ Resubmission after refuse to file? _NA_____
Chemical Classification: (1,2,3 etc.) _____1____
Other (orphan, OTC, etc.) _____

Form 3397 (User Fee Cover Sheet) submitted: [YES] NO

User Fee Status: Paid ___X_____ Exempt (orphan, government) _____
Waived (e.g., small business, public health) _____

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application?

  YES [NO]

  If yes, explain: 3-year exclusivity for new molecular entity

- Does another drug have orphan drug exclusivity for the same indication? YES [NO]

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

  YES [NO]

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES [NO]
  If yes, explain.

- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? [YES] NO
- Was form 356h included with an authorized signature? [YES] NO
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? [YES] NO

  If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A [YES] NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format? All

  Additional comments: None
- If in Common Technical Document format, does it follow the guidance? [N/A] YES NO
- Is it an electronic CTD? [N/A] YES NO
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?
  Additional comments: None
- Patent information submitted on form FDA 3542a? [YES] NO
- Exclusivity requested? [YES], ___3__years NO
- Correctly worded Debarment Certification included with authorized signature? [YES] NO
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.
- Financial Disclosure forms included with authorized signature? [YES] NO
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? [YES] NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? [YES] NO
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.
- List referenced IND numbers: IND 62,536 (HFD-170)

IND 38,838

/

- End-of-Phase 2 Meeting? Date ___8/8/02__ NO
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting? Date _____ NO
  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  [YES] NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? [YES] NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? [N/A] YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A [YES] NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? [N/A] YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  [YES] NO

Chemistry—completed prior to filing with NDA 21-427

- Did applicant request categorical exclusion for environmental assessment? YES NO
  If no, did applicant submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES
  NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO

- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 19, 2004

BACKGROUND: This application is currently being reviewed in HFD-120 (NDA 21-427; PDUFA date is June 25, 2004) for treatment for major depressive disorder. This application was also submitted — — , for stress urinary incontinence (AE issued August 29, 2003). ' —

ATTENDEES: T. Permutt, D. Lee, D. Mellon, S. Thornton, R. Roca, B. Rappaport, E. Duffy, H. Josefburg, A. Meyer, and L. Malandro

ASSIGNED REVIEWERS: MO-Howard Josefburg; D. Christodolou, S. Thornton, D. Lee, M. Sobhan

Discipline	**Reviewer**
Medical:	H. Josefburg
Secondary Medical:	R. Roca
Statistical:	M. Sobhan
Pharmacology:	S. Thornton
Statistical Pharmacology:	N/A
Chemistry:	D. Christodolou
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	D. Lee
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	C. Currier
Regulatory Project Management:	L. Malandro
Other Consults:	K. Bonson (CSS)

Per reviewers, are all parts in English or English translation? [YES] NO
If no, explain:

CLINICAL FILE __X____ REFUSE TO FILE _____

- Clinical site inspection needed: [YES] NO
- Advisory Committee Meeting needed? YES, date if known _____ [NO]
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

[N/A] YES NO

CLINICAL MICROBIOLOGY NA ___X___ FILE _____ REFUSE TO FILE _____

STATISTICS		FILE __X____	REFUSE TO FILE _____
BIOPHARMACEUTICS		FILE __X____	REFUSE TO FILE _____
• Biopharm. inspection needed:			YES NO
PHARMACOLOGY	NA _____	FILE __X____	REFUSE TO FILE _____
• GLP inspection needed:			YES NO
CHEMISTRY		FILE __X____	REFUSE TO FILE _____
• Establishment(s) ready for inspection?			Completed
• Microbiology			YES NO

ELECTRONIC SUBMISSION: Yes
Any comments: Clinical and statistical staff have requested revisions to the electronic data.

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

__X____ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ No filing issues have been identified.

___X___ Filing issues to be communicated by Day 74. See letter in DFS

ACTION ITEMS:

Document filing issues conveyed to applicant by Day 74.

_____
Regulatory Project Manager, HFD-

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/s/

Lisa Malandro
7/30/04 03:59:23 PM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: July 29, 2004

To: Bob Rappaport, M.D., Director
Division of Anesthetic, Critical Care and Addiction Drug Products
(HFD-170)

Through: Deborah B. Leiderman, M.D., Director
Michael Klein, Ph.D., Team Leader
Controlled Substance Staff (HFD-009)

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff (HFD-009)

Consult on: Abuse Potential of Cymbalta (Duloxetine)
NDA 21-733
Eli Lilly and Company

Background

This consult is a review of the abuse potential of the NDA for Cymbalta (duloxetine). Duloxetine is a serotonin/norepinephrine reuptake inhibitor (SNRI) that is proposed as a treatment for diabetic neuropathic pain. Duloxetine is not currently marketed in the U.S. but is also under development for the treatment of depression (NDA 21-427 (Cymbalta); reviewed by HFD-120) and stress urinary incontinence

Recommendations

* Based on available clinical and preclinical data submitted by the Sponsor in the NDA Abuse Potential Package, CSS does not find evidence suggesting abuse liability for duloxetine. Thus, CSS does not recommend that duloxetine be scheduled under the Controlled Substances Act, following its approval for marketing

* CSS previously concluded that duloxetine has no abuse potential in an IND consult to HFD-170 on August 20, 2002.

* The label should reflect this recommendation for unscheduled status.

Conclusions

* Biochemical analyses of central nervous system binding sites submitted in the NDA show that duloxetine binds with high affinity to only two sites: the serotonin transporter and the norepinephrine transporter. Functionally, duloxetine is a reuptake inhibitor at both of these transporter sites.

* Data from behavioral studies with rats and monkeys submitted in the NDA do not show any indication that duloxetine has abuse potential. Duloxetine is not self-administered by monkeys, it does not induce withdrawal/physical dependence in rats, and it does not produce unusual overt behavioral effects.

* Data from clinical trials submitted are not suggestive of any abuse potential from duloxetine. Adverse events, as reported in the Integrated Summary of Safety, do not represent symptoms classically associated with drug abuse. There are similarly no reports of discontinuation due to abuse-related behavioral responses. There is no evidence of withdrawal/physical dependence in studies that included a discontinuation phase.

* The abuse liability package submitted in the NDA does not include any data that are suggestive that duloxetine has abuse potential.

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/s/

Katherine Bonson
7/30/04 11:31:18 AM
PHARMACOLOGIST

Michael Klein
7/30/04 03:05:50 PM
CHEMIST

Deborah Leiderman
8/2/04 10:09:59 AM
MEDICAL OFFICER

Malandro, Lisa

From: Sharon L Hoog [HOOG_SHARON_L@LILLY.COM]
Sent: Thursday, July 22, 2004 2:55 PM
To: Josefberg, Howard
Cc: Malandro, Lisa; Roca, Rigoberto A; Sharon L Hoog
Subject: RE: NDA 21-733 Duloxetine Information Request

Hello Dr. Josefberg,
As I understand the discussions within the team preparing the response, the exception to your requested information derives from the following aspect of the second requested analysis :

Study drop-outs (by any treatment week) should always be classified as 'non-responders' for that treatment week, and all following weeks.

In the prepared response, if data exist from the visit at which discontinuation is initiated, it is used. To be sure we understand one another, perhaps we can put together a discussion after you have had a chance to look at the output of the analyses? The submission is still on track to ship today, and I will be happy to forward to you a courtesy copy via email yet today, so you may begin the assessment at your convenience.

Is this an agreeable approach?

Kindest regards,

Sharon

Sharon L. Hoog, M.D.
Sr. Research Scientist, Regulatory
U.S. Regulatory Affairs
317-276-5220

"Josefberg, Howard"
<JosefbergH@cder.fda.gov>

07/21/2004 05:10 PM

To: "'hoog_sharon_l@lilly.com'" <hoog_sharon_l@lilly.com>, "Malandro, Lisa" <MalandroL@cder.fda.gov>
cc: "Roca, Rigoberto A" <ROCAR@cder.fda.gov>
Subject: RE: NDA 21-733 Duloxetine Information Request

Sharon,

Yes, the July 20 request only. The July 20 request replaces (enhances?) the one from July 19. I'm sorry if there has been confusion.

Which aspect of the request are you referring to (as not being implemented)? I'm happy to speak with you about it, but it might be something that we could sort out quickly by email. Just let me know. Thank you.

Howard Josefberg, M.D.
FDA, CDER, DACCADP

-----Original Message-----
From: Malandro, Lisa
Sent: Wednesday, July 21, 2004 4:57 PM
To: Josefberg, Howard; Roca, Rigoberto A
Subject: FW: NDA 21-733 Duloxetine Information Request

Howard, please confirm your request for the Sponsor, ty, lm
-----Original Message-----
From: Sharon L Hoog [mailto:HOOG_SHARON_L@LILLY.COM]
Sent: Wednesday, July 21, 2004 4:39 PM
To: Malandro, Lisa
Cc: Sharon L Hoog
Subject: Re: NDA 21-733 Duloxetine Information Request

Hello Lisa,
Would you please confirm that the reviewer would like a response only to the information request sent July 20 and not to both it and the request sent July 19? We are preparing to publish for shipment tomorrow.

Also, there is a single aspect of the request that we have not implemented due to its requiring reprogramming of data. While an explanation of this will accompany the output tables, I will be glad to have a conversation about it with Dr. Josefburg in advance. Just let me know.

Thanks very much!

Sharon
Sharon L. Hoog, M.D.
Sr. Research Scientist, Regulatory
U.S. Regulatory Affairs
317-276-5220

"Malandro, Lisa" <MalandroL@cder.fda.gov>

07/20/2004 03:40 PM

To. "'Sharon L Hoog'" <HOOG_SHARON_L@LILLY.COM>
cc: "Malandro, Lisa" <MalandroL@cder.fda.gov>
Subject: NDA 21-733 Duloxetine Information Request

Sharon,

Attached , please find a revisedrequest from the Division related to their ongoing review of the above duloxetine application. Please submit your response to this request in electronic archival format as an amendment to NDA 21-733.

Additionally, could you please clarify what strengths are proposed to be marketed for this application? There seems to be some confusion among the reviewers.

If you have questions, please let me know.

Thank you,

Lisa Malandro

[attachment "Lilly requestJUL20.doc" has been removed by Sharon L Hoog/AM/LLY]

Malandro, Lisa

From: Sharon L Hoog [HOOG_SHARON_L@LILLY.COM]
Sent: Wednesday, July 21, 2004 4:54 PM
To: Malandro, Lisa
Cc: Sharon L Hoog
Subject: Re: NDA 21-733 Duloxetine Information Request

Hello Lisa,
The dose Lilly is proposing for treatment of DNP is 60 mg. However, to accommodate adjustments a physician may wish to make for those who would benefit by a split dose regimen, by dose titration to therapeutic effect, or by possible dose reduction due to comorbidities such as renal impairment, concomitant medications, etc., two lower strengths will be available (20 and 30 mg capsules).

Thanks very much-

Sharon
Sharon L. Hoog, M.D.
Sr. Research Scientist, Regulatory
U.S. Regulatory Affairs
317-276-5220

"Malandro, Lisa" <MalandroL@cder.fda.gov>

07/20/2004 03:40 PM

To: "'Sharon L Hoog'" <HOOG_SHARON_L@LILLY.COM>
cc: "Malandro, Lisa" <MalandroL@cder.fda.gov>
Subject: NDA 21-733 Duloxetine Information Request

[attachment "smime.p7m" has been removed by Sharon L Hoog/AM/LLY]

Malandro, Lisa

From: Malandro, Lisa
Sent: Tuesday, July 20, 2004 4:40 PM
To: 'Sharon L Hoog'
Cc: Malandro, Lisa
Subject: NDA 21-733 Duloxetine Information Request
Importance: High

Sharon,

Attached , please find a revised request from the Division related to their ongoing review of the above duloxetine application. Please submit your response to this request in electronic archival format as an amendment to NDA 21-733.

Additionally, could you please clarify what strengths are proposed to be marketed for this application? There seems to be some confusion among the reviewers.

If you have questions, please let me know.

Thank you,

Lisa Malandro

APPEARS THIS WAY
ON ORIGINAL

Analysis #1 (for the ITT populations in the Acute Phase)
Please tabulate and graph for studies HMAW and HMAVa (separately, and combined)
Within subject, percentage change at endpoint, in the 24-hour average pain score (averaged over the subjects' last seven days, the same as you've done)

For each patient that did not complete the acute treatment phase, that patient's '24-hour average pain score' at endpoint should be equal to their '24 hour average' baseline pain score. The 24-hour average pain score at 'endpoint' should not be calculated based upon their last available 24-hour average pain scores.

Percentage Change ..... (within subject):

Pain Score	Placebo	Duloxetine 20 mg QD	Duloxetine 60 mg QD	Duloxetine 60 mg BID
	n (%)	n (%)	n (%)	n (%)
Any increase				
No change				
> 0% decrease				
≥ 10 % decrease				
≥ 20 % decrease				
≥ 30 % decrease				
≥ 40 % decrease				
≥ 50 % decrease				
≥ 60 % decrease				
≥ 70 % decrease				
≥ 80 % decrease				
≥ 90 % decrease				
= 100% decrease				

APPEARS THIS WAY
ON ORIGINAL

Analysis #2 (for the ITT populations in the Acute Phase)
For both HMAW and HMAVa, separately, please tabulate and graph, by dose, the responder rates (using your definition, =30% decrease in 24-hour average pain score) at each study Week (on treatment, Acute Phase)

At each study Week, for each dose, the percentage of subjects that are classified as 'responders' and as 'sustained responders'

Study drop-outs (by any treatment week) should always be classified as 'non-responders' for that treatment week, and all following weeks.

Responder Rate HMAW/Sustained Responder Rate HMAW

Treatment Week	**Placebo**	**Duloxetine 20 mg QD**	**Duloxetine 60 mg QD**	**Duloxetine 60 mg BID**
	n (%)	**n (%)**	**n (%)**	**n (%)**
1				
2				
3				
4				
5				
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8				
9				
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11				
12				

And repeat for HMAVa

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/s/

Lisa Malandro
7/21/04 09:36:19 AM

Malandro, Lisa

From: Malandro, Lisa
Sent: Monday, July 19, 2004 3:56 PM
To: 'Sharon L Hoog'
Cc: Malandro, Lisa
Subject: NDA 21-733 Duloxetine Information Request

Importance: High

Lilly
iestJUL18.doc (63 K

Sharon,

In the attached Word document, please find additional requests from the Division related to their ongoing review of the above duloxetine application. Please submit your response to these requests in electronic archival format as an amendment to NDA 21-733.

If you have questions, please let me know.

Thank you,
Lisa Malandro

APPEARS THIS WAY
ON ORIGINAL

Lilly request

Analysis #1 (for the ITT populations in the Acute Phase)
Please tabulate and graph for studies HMAW and HMAVa (separately, and combined)
Within subject, percentage change at endpoint, in the 24-hour average pain score
(averaged over the subjects' last seven days, the same as you've done)

Percentage Change in Endpoint (within subject):

Pain Score	**Placebo**	**Duloxetine 20 mg QD**	**Duloxetine 60 mg QD**	**Duloxetine 60 mg BID**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Any increase				
No change				
> 0% decrease				
≥ 10 % decrease				
≥ 20 % decrease				
≥ 30 % decrease				
≥ 40 % decrease				
≥ 50 % decrease				
≥ 60 % decrease				
≥ 70 % decrease				
≥ 80 % decrease				
≥ 90 % decrease				
= 100% decrease				

Analysis #2 (for the ITT populations in the Acute Phase)
For both HMAW and HMAVa, separately, please tabulate and graph, by dose, the responder rates (using your pre-specified definitions) at each study Week (on treatment, Acute Phase)

At each study Week, for each dose, the percentage of subjects that are classified as 'responders' and as 'sustained responders'

Responder Rate HMAW/Sustained Responder Rate HMAW

Treatment Week	**Placebo**	**Duloxetine 20 mg QD**	**Duloxetine 60 mg QD**	**Duloxetine 60 mg BID**
	n (%)	**n (%)**	**n (%)**	**n (%)**
1				
2				
3				
4				
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7				
8				
9				
10				
11				
12				

And repeat for HMAVa

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/s/

Lisa Malandro
7/21/04 09:34:14 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUN 15 2004

Michael A. Turik, M.D.
Indiana University Hospital, RMUH6134
550 North University Boulevard
Indianapolis, Indiana 46202-5250

Dear Dr. Turik:

Between April 12 and May 5, 2004, Dr. Ni Khin, Dr. Robert Stasko, and Ms Leigh Myers, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of two clinical investigations:

Protocol #F1J-LC-HMCG(d), entitled: "A Placebo-Controlled Study of the Electrophysiologic Effects of Supratherapeutic Doses of Duloxetine on the QT Interval", conducted for Eli Lilly & Company

Protocol F1J-LC-SBCH9(a), entitled: "Safety and Tolerance of Duloxetine in Healthy Females at Supratherapeutic Doses Achieved by a Progressive 1- to 3-Day Titration", conducted for Eli Lilly & Company

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report, and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown our personnel during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3004460917
Field Classification: NAI
Headquarters Classification: NAI

cc:
HFA-224
HFD-580/Doc.Rm./IND
HFD-120/Doc. Rm./IND
HFD-580/Division Director/Houn
HFD-120/Division Director/
HFD-580/MO/Johnson
HFD-580/PM/Perrine
HFD-120/MO/Glass/Racoosin
HFD-120/TL/Andreason
HFD-120/PM/Bates
HFD-46/47/c/r/s/ GCP File # 11204
HFD-46/Blay/Khin
HFD-45/Stasko
HFR-CE750/DIB/Dempster
HFR-CE750/BIMO Monitor/Bellamy
HFR-CE7560/Field Investigator/Myers
GCF-1 Seth Ray

r/d:rab/6/1/04; 6/7/04
reviewed:KMU:6/2/04; 6/7/04
f/t: ML: 6/2/04; 6/7/04
O:\rab\turik.doc

Reviewer's Note to Review Division's Medical Officer

An FDA inspection of the above protocols was prompted by a serious adverse event for Protocol #F1J-LC-HMCG(d) in which a subject committed suicide on February 7, 2004. Inspection of the site and relevant documentation of the studies, and interviews with Dr. Turik and staff, revealed no objectionable conditions or remarkable deficiencies

29 subjects were randomized to treatment in study HMCG, and eight subjects discontinued prematurely. The records of 18 subjects were reviewed in depth including the electronic CRFs for several of the subjects. The records for all 12 subjects in study SBCH were briefly reviewed.

There was no evidence of under-reporting of adverse events. Adverse events were entered directly into the electronic data capture system. This system included information regarding time and date of onset of the adverse event, severity, seriousness, duration, relationship to study drug, and outcome. While there was a section in the database to provide additional commentary on the adverse event, no such commentary was observed during the inspection. Dr. Turik stated that he did not include such commentary because he would be unable to view this information once the database was locked. Such commentary would have been helpful for example, in the case of one subject who had an AV block according to his cardiologist but was not followed up because Dr. Turik disagreed with the cardiologist's assessment. Similarly, for another subject who reported hallucinations, additional commentary on the nature of the hallucinations would have been informative. Inclusion of such commentary constituted a discussion point between the FDA investigators and Dr. Turik during the inspection.

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/s/

Khin U
6/18/04 09:16:00 AM

Malandro, Lisa

From: Sharon L Hoog [HOOG_SHARON_L@LILLY.COM]
Sent: Thursday, July 08, 2004 4:25 PM
To: MALANDROL@CDER.FDA.GOV
Cc: Sharon L Hoog
Subject: NDA 21-733 Dataset Question & Answer

Hi Lisa,
1. Regarding the question about HMAVa tables, I have the following explanation from one of our statisticians: We are glad to have a teleconference also, if that makes sense.

The dataset used to create Tables HMAVa 11.9 - HMAVa 11.11 was PAINWKLY. In Table HMAVa 11.12, the first 2 variables (24-Hour Worst Pain Score and 24-Hour Night Pain Score) are located in the dataset PAINWKLY. The rest of the variables in Table 11.12 are in the dataset EFFICACY.

Both of these datasets were sent in with the original submission and with the updated datasets.

2. As for the earlier question regarding what is unique in the DNP NDA, the answer is being cross-checked. We are willing to have a teleconference to explain this as well, if that would be helpful. Just let me know.

For the remainder of the day, I can be reached by my cell phone: 317-430-6420, as I will be away from the office.

Thanks!
Sharon

Sharon L. Hoog, M.D.
Sr. Research Scientist, Regulatory
U.S. Regulatory Affairs
317-276-5220

Malandro, Lisa

From: Sharon L Hoog [HOOG_SHARON_L@LILLY.COM]
Sent: Tuesday, June 29, 2004 11:32 AM
To: Malandro, Lisa
Cc: Sharon L Hoog; Ann Robbins Sakai
Subject: Re: NDA 21-733 Duloxetine Request

Good morning Lisa,

To date, neither of the other NDA's has been updated with results of biopharmaceutical studies.

The status of study requests from the other divisions is as follows:

In its , the DNDP (120) requested dissolution studies to address naphthol formation . This request was made to which Lilly agreed. The time frame for submission of those reports is within three months of approval of the MDD NDA.

As always, let me know if you have any further questions.

Thanks very much-

Sharon
Sharon L. Hoog, M.D.
Sr. Research Scientist, Regulatory
U.S. Regulatory Affairs
317-276-5220

"Malandro, Lisa"
<MalandroL@cder.fda.gov>

06/28/2004 05:09 PM

To: "'HOOG_SHARON_L (HOOG_SHARON_L@LILLY.COM)'" <HOOG_SHARON_L@LILLY.COM>
cc:
Subject: NDA 21-733 Duloxetine Request

Hi Sharon,
Our Biopharmaceutics reviewer asked me to ask you if there has been any update to the NDA with regard to any biopharmaceutical studies requested by the other Divisions.

Thanks,

Lisa

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-733

Lilly Research Laboratories
A Division of Eli Lilly and Company
Eli Lilly Corporate Center
Indianapolis, IN 46285

Attention: Sharon L. Hoog, M.D.
Senior Regulatory Research Scientist
U.S. Regulatory Affairs

Dear Dr. Hoog:

Please refer to your March 2, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cymbalta (duloxetine hydrochloride).

We also refer to your submissions dated April 26, May 5 and May 11, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on May 14, 2004, in accordance with 21 CFR 314.101(a).

We request that you submit the following information:

1. Provide a status update of the Clinical Pharmacology and Biopharmaceutics related deficiences identified in the Approvable letter dated August 29, 2003 for NDA [redacted] for stress urinary incontinence.

2. Clearly identify the new Clinical Pharmacology and Biopharmaceutics information submitted in NDA 21-733 that was not previously submitted to NDA [redacted]

3. Correct and resubmit dataset Q403SAE.XPT, so that each row in the dataset represents one SAE (and each SAE corresponds to a single row, or line listing) as discussed during our May 7, 2004 face-to-face meeting.

4. Provide full CRFs for the following subjects (all were "discontinued due to physician decision")

DNP Program
F1JMCHMAV0030351
F1JMCHMAV0131302

F1JMCHMAW1031445
F1JMCHMAW1143617
F1JMCHMAW1215010

F1JMCHMAY1071710

F1JMCHMBT1021202
F1JMCHMBT1031310
F1JMCHMBT1071708
F1JMCHMBT3013104
F1JMCHMBT6016106
F1JMCHMBT6036301

MDD Program
F1JMCHMAI1331161
F1JMCHMAI2002010
F1JMCHMAI2472492
F1JMCHMAI7217227
F1JMCHMAI9139290

F1JMCHMAQ1172702

F1JMCHMAU1355649
F1JMCHMAU1537414

F1JMCHMAY1071710

F1JMCHMBH1293916

F1JMCHMBO1051523

F1JUSHMCB0014009
F1JUSHMCB0084225
F1JUSHMCB0084235
F1JUSHMCB0134368
F1JUSHMCB0204587
F1JUSHMCB0214604
F1JUSHMCB0244694
F1JUSHMCB0254722

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.

If you have any questions, please call Lisa Malandro, Regulatory Project Manager, at (301) 827-7416.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Bob Rappaport
5/14/04 05:59:59 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-733

Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Attention: Sharon L. Hoog, M.D.
Senior Regulatory Research Scientist,
U.S. Regulator Affairs

Dear Dr. Hoog:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Duloxetine Hydrochloride (LY248686; 20, 30 - 60 mg).

We also refer to your April 26, 2004, correspondence, received April 27, 2004, requesting a meeting to discuss the general progress and status of the pending application review. We have considered your request and have concluded that the meeting is unnecessary. Due to the current issues with the electronic data sets, substantial review of this application has been delayed and there are no current issues to discuss at this time. Any review comments will be relayed to you in a 74-day communication.

If you have any questions, call me at (301) 827-7416.

Sincerely,

{See appended electronic signature page}

Lisa Malandro
Regulatory Health Project Manager
Division of Anesthetic, Critical Care
And Addiction Drug Products, HFD-170
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
5/7/04 03:55:17 PM
for Lisa Malandro

Malandro, Lisa

From: Sharon L Hoog [HOOG_SHARON_L@LILLY.COM]
Sent: Friday, April 23, 2004 6:16 PM
To: MALANDROL@CDER.FDA.GOV
Cc: Sharon L Hoog
Subject: NDA 71-233 Here are the extra data questions

Hi Lisa,
Here are some more questions that have arisen as the group works through the process of reconstructing datasets:

1. We showed an example of the TESS (treatment emergent adverse events) dataset on Tuesday in the meeting. I believe the reviewer asked that we create this dataset at the Study level for the studies that were included in the DNP submission. The DNP pain studies were HMBT, HMAW, and HMAVa. There was an additional study included in the submission, the depression study, HMBC. Please clarify whether or not a TESS dataset is required for HMBC.
2. Regarding the study level TESS files. Please clarify the following: The study level files were used for the analyses in each of the Clinical Study Reports.
   For HMAW - MEDDRA VERSION: 5.1 was used for analysis
   For HMBT - MEDDRA VERSION: 6.1 was used for analysis
   For HMAVa - MEDDRA VERSION: 6.0 was used for analysis

   Our proposal is to add the MedDRA Terms on the TESS files for these studies using the MedDRA version that was used for the analysis of each study.
   Is this acceptable?

   3. Regarding the new variable that we discussed in Tuesday's meeting, "Days on Duloxetine". We want to clarify that this variable will be placed on the TESS file used for the ISS, the integrated database.

Lisa, if I can assist with communications, such as making Peggy available by telephone, I am happy to do so.
Just let me know.

Thanks again,

Sharon
Sharon L. Hoog, M.D.
Sr. Research Scientist, Regulatory
U.S. Regulatory Affairs
317-276-5220

Malandro, Lisa

From: Sharon L Hoog [HOOG_SHARON_L@LILLY.COM]
Sent: Thursday, April 22, 2004 2:42 PM
To: MALANDROL@CDER.FDA.GOV
Cc: Sharon L Hoog; Margaret Peggy J Stamm
Subject: Clarifications regarding datasets NDA:21-733
Follow Up Flag: Follow up
Flag Status: Flagged

Hi Lisa,
Peggy Stamm needs a bit more detail regarding updating the datasets. Would you please ask Dr. Josefburg/Dalpan et al the following?

SPLITTING FILES
The following are options which Peggy would like the reviewers to consider. (Please choose)

Option 1: Splitting the files by Analyte - ALT codes would be in 2 files, AST would be in another 2 files

Option 2: Splitting the files by the database flags, example, Placebo Controlled Primary database, Placebo Controlled Secondary Database, Overall Duloxetine Database. This would be similar to how we are going to split the TESS (Treatment Emergent Adverse Events) file.

Option 3: To further split the Option 2 database by the Lab Groups which were analyzed together. Example Chemistry, Hem Labs, UA labs.

Option 4: To further split the Option 2 database by Analyte - ALT, AST, Calcium, just a few examples.

SEPARATE DATASET
Would the reviewers like a dataset for the Secondary Conditions and Historical Diagnosis Events, since the EVENTS file is being replaced with the TESS files?
Secondary Conditions and Historical Diagnosis, will not be captured in the TESS file unless the severity of the Secondary Condition worsened while the patient was on Study Therapy. Assuming you want this dataset, do you want one file for Secondary Conditions and another one for Historical Diagnosis?

NOTES
Regarding the NOTES which the reviewers asked us to add to the files.
This is a field which is available in JMP to help explain the different variables. The FDA Guidance document states the electronic files should be SAS transport files. This means sending JMP files is not allowed. The field NOTES is not available in SAS files. After speaking with SAS Institute, we determined that the only place on a SAS transport file where detail can be stored is in the LABEL field. The FDA guidance document only allows for 32 characters to be stored in the LABEL. This would also create additional problems while using JMP because the LABEL field on each variable actually is the field name that is displayed when the file is opened using JMP. Detailed descriptions of each variable are currently provided in the Data Definitions. We are also going to update the Data Definitions with suggestions from the reviewer to add more clarity/detail. Lilly proposes that the Data Definitions be used for explanations of the variables on the datasets. We regret that we could not find a way to add the NOTES fields to the datasets. We would like your agreement that this is acceptable.

If a teleconference would be useful, I am sure Peggy would be happy to talk with Dr. Josefburg directly.

I will be calling you shortly about the timing in which various items can be made available.

Thanks Very Much

Sharon
Sharon L. Hoog, M.D.
Sr. Research Scientist, Regulatory
U.S. Regulatory Affairs
317-276-5220

APPEARS THIS WAY
ON ORIGINAL

Malandro, Lisa

From: Malandro, Lisa
Sent: Monday, April 19, 2004 4:45 PM
To: 'HOOG_SHARON_L (HOOG_SHARON_L@LILLY.COM)'
Subject: NDA 21-733 Duloxetine Request from CSS

Importance: High

Contacts: HOOG_SHARON_L

Sharon,
The Controlled Substances Staff has identified the following filing issue. Your response to this request should be made as an amendment to the NDA. The amendment should be received by the Division with enough time for CSS to evaluate your response prior to the filing date (May 1, 2004).

As conveyed at the EOP2 meeting of August 8, 2002, the use of one package for the Abuse Potential material serves the purpose of organizing all of the abuse-related information in one easily retrievable and reviewable volume or one location in the EDR. This has not been included in this application.

CSS specified that the data in the package should address the following categories as related to abuse: Chemistry, pharmacology, PK/PD, the ISS and ISE, information related to overdose and a proposal for scheduling under the CSA if appropriate.

Please contact me if I can be of assistance.

Thank you,

Lisa Malandro

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ON ORIGINAL

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

/s/

Lisa Malandro
4/20/04 01:06:03 PM
CSO

Malandro, Lisa

From: Malandro, Lisa
Sent: Monday, April 19, 2004 2:20 PM
To: 'HOOG_SHARON_L (HOOG_SHARON_L@LILLY.COM)'
Subject: NDA 21-733 Duloxetine

Importance: High

Sharon,
Following is a preliminary list of inconsistancies that Dr. Josefburg has found in the ISS "Events" datasets. Please do not attempt to respond to these by tomorrow. Please contact me with any questions.
Lisa

- According to the Data Definition Tables, the field designated as SEREVNT should be 'Y' or 'N' for events coded as EV, but should have no value, for events coded as SC and HD - Many events coded as SC have a corresponding Y or N value for SEREVNT.
- It appears that "events" coded as EV receive an EVSTATUS value of 'NW' (for new) or 'CF' (for continued), but that "events" coded as SC or HD are not supposed to receive an EVSTATUS value, that is, the corresponding cells should remain empty. This was the case in the major depressive disorder NDA (MDD) datasets, where the only events assigned NW (or CF for that matter), were those coded as EV;); "events" coded as HD (historical diagnosis) or as SC (secondary conditions) were not assigned values for EVSTATUS. Unfortunately, in the NDA 21-733 data, some (but not all) SC "events" have corresponding EVSTATUS values (of NW or CF), making identification of the actual adverse events difficult. In some cases "events" coded as SC (for EVENTTYP) with "date-of-onset" many years in the past, contain an 'NW' value for EVSTATUS, for reasons that are unclear.
- Values are often missing for BODYSYSC and BODYSYST. For example, all rows (in the integrated datasets) for the two efficacy studies (HMAW, HMAVa), their OL follow-up(s) and the long-term OL safety study (HMBT). BODYSYSC/BODYSYST values are also missing as for a number of the other studies. According to the Data Definitions Tables, these two fields should be populated in the ISS 'Events' datasets. The definitions tables also indicate that the sponsor did not intend to populate these fields, for the 'Events' datasets within the individual study folders. They aren't, but they should be...at least for all studies (subjects) included in the primary safety database
- The EVENT field is also often not populated, in both the ISS and the individual study 'Events' datasets.
- Some "events" coded as "EV" sound as if they would have more appropriately been coded as SC (or HD). Examination of the data alone often makes it very difficult to ascertain whether, and when patients experienced treatment-emergent exacerbations of chronic conditions. For instance in ISS dataset E002004:
  - Patient HMBHA-2302 has one line listing with the ACTTERM 'RECURRENT HEADACHES' and values of EV (EVENTTYP), NW (EVSTATUS), 9 (VISIT), 1 (EVENTSEQ), 25 (EVENTID) and 1964 for ONSETCDT. The same patient has another line listing with the ACTTERM 'RECURRENT HEADACHES' with the values SC (EVENTTYP), 1 (VISIT), 1 (EVENTSEQ), 6 (EVENTID), 1964 for ONSETCDT, but with a missing value for the EVSTATUS field.
  - HMAW patient 2814 has DIARRHEA (ONSETCDT = 1980) and LEG SWELLING and ANGINA (ONSETCDT = 1996) all coded as EV (and CF).
  - HMAW-2820 has ACTTERM 'ARTHRITIS' (ONSETCDT = 1987) with EVENTTYP EV.
  - HMAW-2822 has ACTTERM 'BACK PAIN' with ONSETCDT = 1964, NW at VISIT 13, CF at VISIT 15.
  - HMAW-2823 has the ACTTERM 'OSTEOARTHRITIS' with ONSETCDT = 1976, which is EVENTTYP = SC at VISIT = 1 (EVSTATUS missing). HMAW-2823 also has OSTEOARTHRITIS as an NW (EVSTATUS) at VISIT = 3, also with ONSETCDT = 1976, and then many listings of OSTEOARTHRITIS as CF (EVSTATUS) from VISIT = 4, all with ONSETCDT = 1976.

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

/s/

Lisa Malandro
4/20/04 01:03:42 PM
CSO

Malandro, Lisa

From: Sharon L Hoog [HOOG_SHARON_L@LILLY.COM]
Sent: Friday, April 16, 2004 5:14 PM
To: MALANDROL@CDER.FDA.GOV
Cc: Sharon L Hoog
Subject: NDA 21-733 trip to Rockville

Hello Lisa,
Thank you again for organizing a very useful meeting.

1. I will forward our draft minutes from the T-con, likely Monday morning. They will contain the list of participants from Indianapolis and their function.

2. As I said in my voicemail, three technical experts and I are making arrangements to be there Tuesday afternoon per our discussion today. We will have a plan to demonstrate the new parameters, and assist the reviewers in navigating the new TESS datasets, answer questions, resolve snags etc. Also, we are working to have a primer on the pharmacology database, which is different

3. In order to be technically ready, we would appreciate approximately a half hour visit with you in advance of the meeting with the Reviewers to be sure all the lines are live. If it is not possible on Monday or earlier on the day Tuesday, may we do this immediately prior to the session with the Reviewers?

4. Also, if the fax of potential quality issues gets to us on Monday, it may be possible for us to have some responses prepared by Tuesday as well.

Thanks and I 'll talk to you soon.

Sharon

Sharon L. Hoog, M.D.
Sr. Research Scientist, Regulatory
U.S. Regulatory Affairs
317-276-5220

Malandro, Lisa

From: Sharon L Hoog [HOOG_SHARON_L@LILLY.COM]
Sent: Thursday, April 15, 2004 1:05 PM
To: MALANDROL@CDER.FDA.GOV
Cc: Sharon L Hoog
Subject: NDA 21-427 Dataset requests, activity update and FYI about 90-day conference

Hello Lisa,

DATASETS
Since our teleconference on Monday, representatives from statistics, IT, medical, clinical pharmacology, systems, project management, submission coordination and regulatory have been working on the dataset issues identified by the DACCADP reviewers. While we believe we have some straight forward solutions, we need some clarification of details of the requests to be confident that updated integrated datasets or other solutions will deliver what is needed. Also, where there are limitations or variations we would like to have them clearly understood.

I am compiling the list of Lilly people who have clarification questions, and will forward their technical titles to you in hopes that in the very near future, we can facilitate a conversation between them and their FDA counterparts.

I suspect that your reviewers are very busy, and we are earnestly striving to resolve this satisfactorily and in a short time frame.
I am sensitive to the timing of the filing meeting and other milestones coming up.

90-DAY CONFERENCE
Also, for your planning purposes, we will be requesting the 90-day conference. Once I have confirmed any "blackout" dates for key personnel, I will notify you and send that meeting request letter.

As always, thanks very much for your help.

Sharon

Sharon L. Hoog, M.D.
Sr. Research Scientist, Regulatory
U.S. Regulatory Affairs
317-276-5220

Malandro, Lisa

From: Sharon L Hoog [HOOG_SHARON_L@LILLY.COM]
Sent: Monday, April 12, 2004 4:48 PM
To: MALANDROL@CDER.FDA.GOV
Cc: Sharon L Hoog
Subject: NDA 21-733 location of abuse potential info

Hello Lisa,

I have two references for you here.
First, the Abuse Potential topic is addressed in the Clinical Overview, Section 2.5.5.8
Second, the direct path to the toxicology report is:

Pharm Tox Table of Contents
Toxicology Study Reports
Supplemental Toxicity Study Reports
Antigenicity and Dependence Studies
Note to Reviewer and Report #41

The location is driven by the fact that the majority of the tox information is cross-referenced to NDA 21-427. Reviewers asked that we duplicate this report for NDA 21-733.

Thanks very much-

Sharon

Sharon L. Hoog, M.D.
Sr. Research Scientist, Regulatory
U.S. Regulatory Affairs
317-276-5220

45 DAY MEETING CHECKLIST
(Answer Yes or No to the questions below)

FILEABILITY:

On initial overview of the NDA application:

STATISTICAL:

(1) On its face, is the statistical section of the NDA organized in a manner to allow substantive review to begin? yes

(2) Is the statistical section of the NDA indexed and paginated in a manner to allow substantive review to begin? yes

(3) On its face, is the statistical section of the NDA legible so that substantive review can being? yes

(4) On its face, do there appear to be at least two adequate and well-controlled studies in the application? yes

(5) Are the pivotal efficacy studies of appropriate design to meet the basic requirements for approvability of this product based on proposed draft labeling? yes

(6) Are all the data sets for pivotal efficacy studies 'complete for all indications (infections) requested? yes

(a) Line listings by Center

(b) Intermediate analysis summary tables

(c) Pathogen listing

(d) Adverse events listing by Center

(e) Lost subject/patient tables by reason, time of loss, and center

(7) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? yes

(8) From a statistical perspective, is this NDA fileable? If "no", please state below why it is not. yes

_____

Reviewing Statistician Date

_____

Supervisory Statistician Date

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

/s/

Thomas Permutt
4/8/04 04:14:24 PM
BIOMETRICS

Office of Drug Safety

MEMO

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

From: Tia M. Harper-Velazquez, Pharm.D.
Safety Evaluator, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

Through: Alina R. Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

Carol A. Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

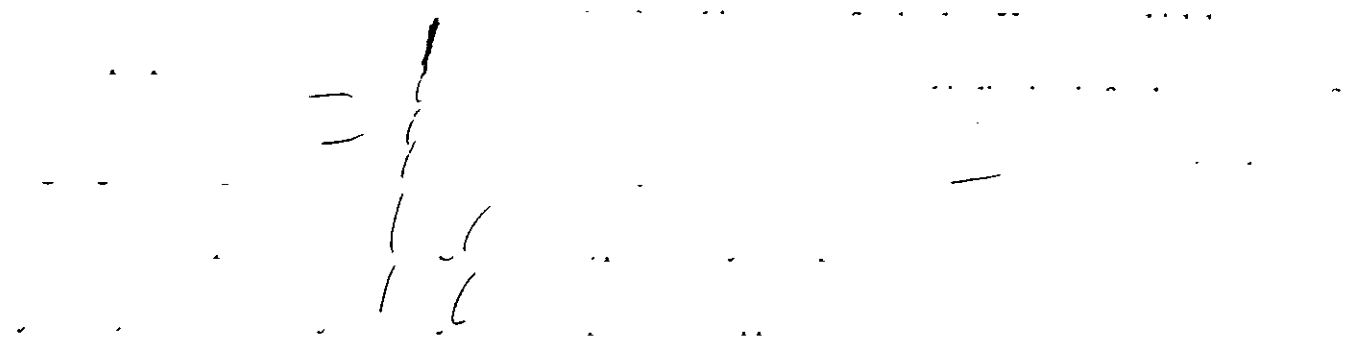
CC: Doris Bates
Project Manager, Division of Neuropharmacological Drug Products
HFD-120

Date: March 3, 2004

Re: ODS Consult 01-0167-3, Cymbalta (Duloxetine Hydrochloride Capsules) 20 mg, 30 mg, — 60 mg; NDA 21-427.

This memorandum is in response to a February 10, 2004, request from your Division for a re-review of the proprietary name, Cymbalta. The proposed proprietary name was previously found acceptable by DMETS on September 13, 2002 (ODS Consult # 01-0167), and July 9, 2003 (ODS Consult # 01-0167-1).

Since those reviews, DMETS has not identified any additional proprietary or established names that have the potential for confusion with Cymbalta that would render the name objectionable. However, in our reviews dated April 23, 2003 (ODS Consult # 03-0012), and July 11, 2003 (ODS Consult # 03-0012-1), DMETS noted the potential for confusion between Cymbalta and Symbyax due to sound-alike similarities. Symbyax and Cymbalta share the same beginning sounds ("Symb" vs. "Cym"), however, the remainder of the names are phonetically and orthographically different ("yax" vs. "alta"). Symbyax is a combination product containing olanzapine and fluoxetine, and is available in multiple strengths (3 mg/25 mg, 6 mg/25 mg, 6 mg/50 mg, 12mg/25mg, and 12 mg/50 mg, whereas Cymbalta contains a single ingredient (fluoxetine), and will be available in strengths of 20 mg, 30 mg - 60 mg. Both products are available as oral capsules for once daily administration. Additionally, Symbyax and Cymbalta are both sponsored by Eli Lilly, and therefore, may share similarities in labeling and packaging. If approved, Cymbalta will be launched into the marketplace soon after the approval of Symbyax, which as approved by the Agency on December 23, 2004. Confusion may be further compounded as a result of similarities in the established names (fluOXETINE vs. duLOXETINE). Therefore, DMETS continues to recommend that efforts be made to differentiate the packaging between Cymbalta and Symbyax. The sponsor should also develop an educational campaign which would emphasize the differences between these two products at the time of approval.



In summary, DMETS has no objection to the use of the proprietary name provided the sponsor ensures differentiation in packaging between Cymbalta and Symbyax, and institutes an educational campaign that will educate practitioners and patients concerning the differences of Cymbalta and Symbyax. We consider this a final review. If the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from this date forward. We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: December 31, 2006.

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

2. TELEPHONE NUMBER *(Include Area Code)*

(317) 277-3799

3. PRODUCT NAME

Duloxetine Hydrochloride

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 21-733

5 DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW.

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____ (APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4674

7 IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

8 HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FORTHIS APPLICATION?

☐ YES ☒ NO

(See item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
	Gregory T. Brophy, Ph.d. Director, U.S. Regulatory Affairs	3/2/2004

FORM FDA 3397 (12/03)

PSC Media Arts (301) 443-1090 EF

Malandro, Lisa

From: Beam, Sammie
Sent: Thursday, June 03, 2004 10:34 AM
To: Malandro, Lisa
Subject: Cymbalta NDA 21-733 Request for consultation



01-0167-3.Cymbalt a.Memo.Final....
01-0167-1CYMBALT A.FIN.doc (36 ...
01-0167.Cymbalta. doc (641 KB)

I have attached a copy of the previous reviews we have finished for Cymbalta in HFD-120. A team leader has reviewed the electronic files for NDA 21-733 and finds them identical to the ones already reviewed for NDA 21-427. Therefore, you may use these documents for NDA 21-733 and consider the name acceptable as long as the product is approved by the end of June.

Please contact me if you have any questions,

Thanks,
Sammie Beam
Project Manager, DMETS

APPEARS THIS WAY
ON ORIGINAL

Format of Financial Disclosure Information

The Financial Disclosure information is provided by study (alphabetically, based on last four characters of study code). As requested by FDA, tables are provided for each of the studies listing investigators (including sub-investigators), status of disclosure, and the number of patients enrolled at each site. We have also defined the due diligence used to obtain the information. Since all three covered studies did not require disclosure, the FDA Form 3454 is presented prior to the tables, certifying that each investigator had nothing to disclose or for whom disclosure was not obtained. In cases where disclosure information was not obtained, the reason for this is stated.

Due Diligence Process for Collection of Financial Disclosure Information

Prior to the beginning of each site's participation in the trial, a cover letter and form were sent to each investigator (including principal investigator, co-investigator, and sub-investigators, hereinafter referred to as "investigator"). The cover letter provided background information regarding the FDA regulation. The form requested consent from the investigator for the transfer of the investigator's relevant financial information to Lilly. If any investigator fails to return the form, the CRO makes follow-up requests.

Following the last patient visit for the study, an additional letter and form were sent to each investigator. This form requests certain financial information. This letter reminds the investigator to provide Lilly with updates and indicates the exact date when the reporting period ends for the particular study (i.e. one-year after the date of the last patient visit for the study). If an investigator fails to return the form, the CRO makes follow-up requests.

If the information is not obtained following numerous requests, specific documentation is noted and filed appropriately in the study files.

Page 6 Blank

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	
See Attached Listing F1J-MC-HMAV(a)	
See Attached Listing F1J-MC-HMAW	
See Attached Listing F1J-MC-HMBT	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
John R. Hayes, M.D.	Duloxetine-Fluoxetine Product Team Leader
FIRM/ORGANIZATION: Eli Lilly & Company	
SIGNATURE	DATE: 12/8/03

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

Created by Electronic Document Services/USDHHS (301) 443-2454 EF

Study F1J-MC-HMAV(a)

Site Name and Number	Number of Patients Enrolled (V1)	Names of Investigators (principal and sub-investigators)	*Certification and/or Disclosure for each Investigator (yes/no)	Disclosable Information (yes/no)
Elizabeth Barranco Site #402	26	Elizabeth Barranco /	Yes Yes Yes	No No No
Lissette Jimenez Site #401	31	Lissette Jimenez /	Yes Yes Yes	No No No

APPEARS THIS WAY
ON ORIGINAL

Duloxetine FDA Form 3454 Attachment

*Staff no longer employed at site, certified letter sent if address was known, financial disclosures not obtained prior to leaving.

**Unable to obtain financial disclosure documents after due diligence was exercised, including certified letter.

***Disclosure not required due to not participating in study.

Study F1J-MC-HMAV(a)

Site Name and Number	Number of Patients Enrolled (V1)	Names of Investigators (principal and sub-investigators)	*Certification and/or Disclosure for each Investigator (yes/no)	Disclosable Information (yes/no)
Cecil, John Site #17	34	John Cecil	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes *No Yes Yes Yes Yes	No No No No No No No No No No No No No No No
Charles, M. Arthur Site #5	8	M. Arthur Charles	Yes Yes *No Yes Yes Yes	No No No No No No
Conway, Martin Site #7	13	Martin Conway	Yes Yes Yes Yes Yes Yes Yes Yes *No Yes	No No No No No No No No No No
Disciglio, Michael Site #8	12	Michael Disciglio	Yes *No Yes Yes *No Yes	No No No No No No

Duloxetine FDA Form 3454 Attachment

*Staff no longer employed at site, certified letter sent if address was known, financial disclosures not obtained prior to leaving.

**Unable to obtain financial disclosure documents after due diligence was exercised, including certified letter.

***Disclosure not required due to not participating in study.

Study F1J-MC-HMAV(a)

Site Name and Number	Number of Patients Enrolled (V1)	Names of Investigators (principal and sub-investigators)	*Certification and/or Disclosure for each Investigator (yes/no)	Disclosable Information (yes/no)
Farmer, Mildred Site #31	3	Mildred Farmer	Yes Yes Yes *No Yes Yes Yes	No No No No No No No
Fried, David Site #10	6	David L. Fried	Yes Yes Yes	No No No
Gilderman, Larry Site # 11	26	Larry Gilderman	Yes Yes Yes Yes	No No No No
Hutchinson, Julia Site #13	20	Julia M. Hutchinson	Yes *No Yes ***No ***No Yes Yes	No No No No No No No
Kluge, Ronica Site #15	13	Ronica Kluge	Yes Yes Yes Yes Yes	No No No No No
Liljenquist, John Site #30	54	John E. Liljenquist	Yes Yes Yes Yes	No No No No

Duloxetine FDA Form 3454 Attachment

*Staff no longer employed at site, certified letter sent if address was known, financial disclosures not obtained prior to leaving.
**Unable to obtain financial disclosure documents after due diligence was exercised, including certified letter.
***Disclosure not required due to not participating in study

Study F1J-MC-HMAV(a)

Site Name and Number	Number of Patients Enrolled (V1)	Names of Investigators (principal and sub-investigators)	*Certification and/or Disclosure for each Investigator (yes/no)	Disclosable Information (yes/no)
Osei, Kwame Site #16	4	Kwame Osei 	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes	No No No No No No No No No No No No
Rankin, Bruce Site #19	23	Bruce G. Rankin 	Yes Yes Yes Yes Yes Yes	No No No No No No
Russell, I. Jon Site #21	12	Jon Russell 	Yes Yes Yes Yes	Yes No No No
Sachson, Richard Site #22	29	Richard Sachson 	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes	No No No No No No No No No No

Duloxetine FDA Form 3454 Attachment

*Staff no longer employed at site, certified letter sent if address was known, financial disclosures not obtained prior to leaving.

**Unable to obtain financial disclosure documents after due diligence was exercised, including certified letter

***Disclosure not required due to not participating in study.

Study F1J-MC-HMAV(a)

Site Name and Number	Number of Patients Enrolled (V1)	Names of Investigators (principal and sub-investigators)	*Certification and/or Disclosure for each Investigator (yes/no)	Disclosable Information (yes/no)
Sharp, Stephan Site #24	16	Stephan Sharp	Yes Yes Yes Yes	No No No No
Sievert, Rubens Site #25	16	Rubens Sievert	Yes Yes Yes Yes Yes	No No No No No
Smith, Tim Site #26	57	Timothy R. Smith	Yes Yes Yes Yes Yes Yes Yes	No No No No No No No
Soler, Norman Site #27	21	Norman Soler	Yes Yes	No No
Lawrence Sherman Site #28 **was replaced by Sherman**	12	Lawerence Sherman	Yes Yes ***No ***No Yes Yes	No No No No No No
Weinstein, Richard Site #29	31	Richard Weinstein	Yes Yes Yes Yes Yes Yes	Yes No No No No No
Zwick, Andrew Site #32	8	Andrew Zwick	Yes Yes Yes Yes Yes Yes	No No No No No No

Duloxetine FDA Form 3454 Attachment

*Staff no longer employed at site, certified letter sent if address was known, financial disclosures not obtained prior to leaving.

**Unable to obtain financial disclosure documents after due diligence was exercised, including certified letter

***Disclosure not required due to not participating in study.

Study F1J-MC-HMAW

Site Name and Number	Number of Patients Enrolled (V1)	Names of Investigators (principal and sub-investigators)	*Certification and/or Disclosure for each Investigator (yes/no)	Disclosable Information (yes/no)
Hospital Francés Site #504	21		Yes Yes Yes	No No No
Hospital "Carlos Durand" Site #505	22		Yes Yes Yes	No No No

Study F1J-MC-HMAW

Site Name and Number	Number of Patients Enrolled (V1)	Names of Investigators (principal and sub-investigators)	*Certification and/or Disclosure for each Investigator (yes/no)	Disclosable Information (yes/no)
Vera Bril Site #500	56	Bril, Vera	Yes Yes Yes Yes Yes Yes Yes	Yes No No No No No No
Elizabeth Barranco Site #502	49	Elizabeth Barranco	Yes Yes	No No

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Study F1J-MC-HMAW

Site Name and Number	Number of Patients Enrolled (V1)	Names of Investigators (principal and sub-investigators)	*Certification and/or Disclosure for each Investigator (yes/no)	Disclosable Information (yes/no)
Ayala, Ricardo Site #101	27	Ricardo Ayala	Yes Yes Yes Yes Yes Yes	No No No No No No
Baumel, Samuel Site #102 Site #202	 31 28	Samuel Baumel	Yes Yes Yes Yes Yes Yes Yes ***No Yes Yes **No Yes Yes Yes Yes Yes **No Yes Yes Yes Yes Yes	No No No No No No No No No No No No No No No No No No No No No No No
Blonsky, Richard Site #103	49	Richard Blonsky	Yes Yes *No *No *No	No No No No No

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Study F1J-MC-HMAW

Site Name and Number	Number of Patients Enrolled (V1)	Names of Investigators (principal and sub-investigators)	*Certification and/or Disclosure for each Investigator (yes/no)	Disclosable Information (yes/no)
Bergstrom, Richard Site #104	19	Richard Bergstrom	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes	No No No No No No No No No No No No No
Petit, William Site #105	16	William Petit	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes *No	No No No No No No No No No No No No
Conway, Martin Site #106	19	Martin Conway	Yes *No Yes Yes Yes Yes Yes Yes Yes	No No No No No No No No No

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Study F1J-MC-HMAW

Site Name and Number	Number of Patients Enrolled (V1)	Names of Investigators (principal and sub-investigators)	*Certification and/or Disclosure for each Investigator (yes/no)	Disclosable Information (yes/no)
Drucker, Jerry Site #107	22	Jerry Drucker	Yes Yes Yes Yes *No Yes Yes Yes *No Yes	No No No No No No No No No No
DeRossett, Sarah Site #108	28	Sarah De Rossett	Yes Yes Yes Yes Yes Yes Yes Yes	No No No No No No No No
Kaplan, Roy Site #109	20	Roy Kaplan	Yes Yes *No Yes Yes Yes *No Yes Yes *No Yes Yes	No No No No No No No No No No No No

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Study F1J-MC-HMAW

Site Name and Number	Number of Patients Enrolled (V1)	Names of Investigators (principal and sub-investigators)	*Certification and/or Disclosure for each Investigator (yes/no)	Disclosable Information (yes/no)
Licata, Angelo Site #110	32	Angelo Licata	Yes Yes Yes Yes Yes Yes *No Yes Yes Yes Yes Yes	No No No No No No No No No No No No
Pellegrino, Richard Site #112	21	Richard Pellegrino	Yes Yes Yes Yes *No Yes *No Yes *No *No	No No No No No No No No No No
Rubin, Michael Site #113	29	Michael Rubin	Yes Yes Yes Yes	No No No No
Sachson, Richard Site #114	31	Richard Sachson	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes	No No No No No No No No No No

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Study F1J-MC-HMAW

Site Name and Number	Number of Patients Enrolled (V1)	Names of Investigators (principal and sub-investigators)	*Certification and/or Disclosure for each Investigator (yes/no)	Disclosable Information (yes/no)
Smith, Tim Site #116	79	Timothy Smith	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes	No No No No No No No No No No No
Soler, Norman Site #117	32	Norman Soler	Yes Yes Yes Yes	No No No No
Troupin, Barbara Site #118	31	Barbara Troupin	Yes ***No Yes Yes ***No ***No ***No ***No ***No Yes ***No Yes ***No ***No ***No Yes	No No No No No No No No No No No No No No No No

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Study F1J-MC-HMAW

Site Name and Number	Number of Patients Enrolled (V1)	Names of Investigators (principal and sub-investigators)	*Certification and/or Disclosure for each Investigator (yes/no)	Disclosable Information (yes/no)
Weinstein, Richard Site #119	38	Richard Weinstein	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes	Yes No No No No No No No No No No No No No No No No No No No
Wendt, Jeanette Site #120	28	Jeanette Wendt	Yes *No *No Yes Yes Yes Yes Yes Yes Yes *No Yes	No No No No No No No No No No No No
Engel, Samuel Site #121	20	Samuel Engel	Yes Yes Yes Yes Yes Yes	No No No No No No

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Study F1J-MC-HMBT

Site Name and Number	Number of Patients Enrolled (V2)	Names of Investigators (principal and sub-investigators)	*Certification and/or Disclosure for each Investigator (yes/no)	Disclosable Information (yes/no)
Rosa Maria de Abreu Vargas Site #400	17	Vargas, Rosa Maria	Yes Yes	No No
Ivan Ferraz Site#401	13	Ferraz, Ivan	Yes Yes Yes	No No No
Adriana Costa e Forti Site #402	24	Forti, Adriana	Yes Yes Yes Yes	No No No No
Joaquim Ignácio Silveira da Mota Neto Site #403	19	Mota Neto, Joaquim	Yes Yes	No No
Helena Schmid Site #405	10	Schmid, Helena	Yes Yes	No No
Marcos Antonio Tambascia Site #406	13	Tambascia, Marcos	Yes Yes Yes	No No No
Manuel Jacobsen Teixeira Site #407	15	Teixeira, Manoel	Yes Yes	No No

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Study F1J-MC-HMBT

Site Name and Number	Number of Patients Enrolled (V2)	Names of Investigators (principal and sub-investigators)	*Certification and/or Disclosure for each Investigator (yes/no)	Disclosable Information (yes/no)
Jorge Alvariñas Site # 300	8	Jorge Alvariñas /	Yes Yes Yes Yes Yes	No No No No No
Alberto Dubrovsky Site # 301	13	Alberto Dubrovsky /	Yes Yes Yes Yes	No No No No
Claudia Goycoa Site #302	11	Claudia Goycoa /	Yes Yes Yes	No No No
Mauricio Jadzinsky Site #303	11	Mauricio Jadzinsky /	Yes Yes Yes	No No No
León E Litwak Site #304	9	León Litwak /	Yes Yes *No	No No No
Pedro Tesone Site #305	11	Pedro Tesone /	Yes Yes Yes Yes	No No No No
Amilcar Sosa Site #306	16	Amilcar Sosa /	Yes Yes	No No

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Study F1J-MC-HMBT

Site Name and Number	Number of Patients Enrolled (V2)	Names of Investigators (principal and sub-investigators)	*Certification and/or Disclosure for each Investigator (yes/no)	Disclosable Information (yes/no)
Jose Luis Castillo Site #500	6	Castillo, Jose Luis	Yes Yes Yes Yes	No No No No
Vicente Gutierrez Site #501	10	Gutierrez, Vicente	Yes Yes Yes Yes	No No No No
Nestor Soto Site #502	13	Soto, Nestor	Yes Yes Yes Yes	No No No No

APPEARS THIS WAY ON ORIGINAL

Duloxetine FDA Form 3454 Attachment

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Study F1J-MC-HMBT

Site Name and Number	Number of Patients Enrolled (V2)	Names of Investigators (principal and sub-investigators)	*Certification and/or Disclosure for each Investigator (yes/no)	Disclosable Information (yes/no)
Chen Ching-Chu Site #600	15	Chen, Ching-Chu	Yes Yes Yes Yes Yes	No No No No No
Cheng Chi-Yuan Site #601	15	Cheng, Chi-Yuan	Yes Yes Yes Yes	No No No No
Lin Jen-Der Site #602	15	Lin, Jen-Der	Yes Yes Yes	No No No
Tu Shih-Te Site #603	17	Tu, Shih-Te	Yes Yes Yes Yes Yes Yes	No No No No No No

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning Richard Weinstein, M.D. (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study (ies): FLI-MC-HMAV(a) and (*Name of clinical study*) FLI-MC-HMAW, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

any proprietary interest in the product tested in the covered study held by the clinical investigator;

any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
John R. Hayes, M.D.	Duloxetine-Fluoxetine Product Team Leader
FIRM/ORGANIZATION: Eli Lilly & Company	
SIGNATURE	DATE: 12/16/2003

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3455 (3/99)

Created by Electronic Document Services/USDHHS (301) EP

Financial Disclosure Form 3455 Supplemental

04Dec2003

RE: Accrued Equity Above Suggested Limits

In review of financial disclosures requested from participating site for Duloxetine study [redacted] it was noted that site [redacted] has accrued a significant equity interest as defined in 21 CFR 54.2(b). Dr. [redacted] reported to Lilly that he held $55,000 in Lilly stock during the period of October 2002 to November 2003.

Dr. [redacted] was one of [redacted]

[redacted] His site enrolled [redacted] patients. This was < 4% of the total patients to be enrolled to the study (N= [redacted]. For these [redacted] patients, it is viewed, from a statistical analysis perspective, the data from this site was consistent in general with the overall pattern. The impact of this one site on the overall study data is insignificant.

APPEARS THIS WAY
ON ORIGINAL

Financial Disclosure Form 3455 Supplemental

11-Dec-03

RE: Accrued Equity Above Suggested Limits

In review of financial disclosures requested from participating site for Duloxetine study — , it was noted that site — Dr — has accrued a significant equity interest as defined in 21 CFR 54.2(b). Dr. — reported to Lilly that he held $55,000 in Lilly stock during the period of June 2001 to December 2003.

Dr. — was one of — number of investigators) in

His site enrolled — patients. This was 3.5% of the total patients to be enrolled to the study (N= — . For these — patients, it is viewed, from a statistical analysis perspective; the data from this site was consistent in general with the overall pattern. The impact of this one site on the overall study data is insignificant.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

D/1 - NDA meeting minutes
8/26/03

IND 62,536

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Attention: Sharon Hoog, M.D.
Senior Regulatory Research Scientist
U.S. Regulatory Affairs

Dear Dr. Hoog:

Please refer to the meeting between representatives of your firm and FDA on July 30, 2003. The purpose of the meeting was to discuss the content and format of a New Drug Application (NDA) for Duloxetine Hydrochloride (LY248686) for [redacted] (DNP).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7407.

Sincerely,

{See appended electronic signature page}

Lisa Marie Malandro
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Industry Meeting Minutes

Date/Time: July 30, 2003 / 1:30 pm **Location:** Parklawn, Conference Room C

Application: IND 62,536

Sponsor: Eli Lilly and Company

Drug/Dosage Form/Doses: Duloxetine HCl (LY248686)/ oral / various

Indication: ---

Type of Meeting: Pre-NDA / Type B

Meeting Chair: Sharon Hertz, M.D., Team Leader, Analgesics
Minutes Recorder: Lisa M. Malandro, Regulatory Project Manager

Sponsor Attendees	Title
Gregory T. Brophy, Ph.D.	Director, U.S. Regulatory Affairs
Sharon L. Hoog, M.D.	Senior Research Scientist, U.S. Regulatory Affairs
John L. Hayes, M.D.	Product Team Leader, Joint Antidepressant Group
Joachim F. Wernicke, M.D., Ph.D.	Senior Clinical Research Physician
Yili Lu, Ph.D.	Research Scientist, Statistics
Amy Rosen, M.S.	Associate Senior Statistician
Smriti Iyengar, Ph.D.	Senior Biologist, Neuroscience Research
David S. Small, Ph.D.	Research Scientist, PK/PD & Trial Simulation
Michael Skinner, M.D.	Clinical Pharmacology
Jole O. Rodriguez, M.S.	Regulatory Affairs, CM&C
---	Associate Consultant, Regulatory Affairs
---	Senior Information Consultant
FDA Attendees	**Title**
Bob Rappaport, M.D.	Acting Director
Dale Koble, Ph.D.	Team Leader, Chemistry
Timothy McGovern, Ph.D.	Team Leader, Pharmacology/Toxicology
Suresh Doddapaneni, Ph.D.	Team Leader, Biopharmaceutics
Sharon Hertz, M.D.	Team Leader, Analgesics
Tom Permutt, Ph.D.	Team Leader, Statistics
Ravi Harapanhalli, Ph.D.	Chemistry Reviewer
Daniel Mellon, Ph.D.	Pharmacology/Toxicology Reviewer
Suliman Al Fayoumi, Ph.D.	Clinical Pharmacology Reviewer
Shaun Comfort, M.D.	Clinical Reviewer
Katherine Bonson, Ph.D.	CSS Reviewer
Paul Andreason, M.D.	HFD-120, Clinical Reviewer
Lisa M. Malandro	Regulatory Project Manager
Pratibha Rana, M.S.	Regulatory Project Manager
Mary Wiley	Epidemiologist
Sandra Birdsong	Project Manager, HFD-430
Martin Pollock	Safety Evaluator, HFD-430
Gary Gensinger	IT Specialist, HFD-001

Meeting Objective(s): To discuss the content and format of a New Drug Application (NDA) for Duloxetine Hydrochloride (LY248686) for — (DNP).

General Discussion: Following introductions, the discussion focused on the Sponsor's questions that were included in the June 26, 2003, meeting package. The Sponsor's questions are presented below in italicized text. Agency responses, prepared prior to the meeting and presented on slides, are bolded. Discussion is presented in normal text.

Question 1: Does HFD-170 agree to allow HFD-120 to be the lead reviewer for the CMC, Clinical Pharmacology and Biopharmaceutics, and Non-clinical Pharmacology and Toxicology sections of the DNP NDA and for specific Study Reports submitted only to NDA 21-427 —

Further, does HFD-170 agree to work with the FDA Electronic Document Room and Lilly to utilize a process of cross-referencing prior NDA's to streamline the DNP NDA review as outlined in the meeting package?

FDA RESPONSE:

CMC: Yes, but there may be indication-specific issues on impurity specifications based on the maximum daily dose.

The Sponsor clarified that the maximum dose — and stated that the specifications previously established will cover this dose. Dr. Harapanhalli stated that the Sponsor will have to adjust the specifications in the event that the maximum dose —.

- **Pharmacology/Toxicology Response: Yes**
  - **— Study reports will be reviewed for any population specific concerns.**
  - **— Nonclinical pharmacology and toxicology comments regarding impurities in the approvable letter issued by HFD-120 should be addressed adequately in the DNP NDA.**
  - **— Any nonclinical pharmacology and toxicology comments made by HFD-580 should be addressed adequately in the DNP NDA.**

- **Clinical Pharmacology Response: Yes.**
  Indication-specific issues include drug-drug interactions and PK in DN patients.

- **Clinical: Yes.**

Question 2:

a. Is the proposal to submit the NDA in the format described in the meeting package acceptable to HFD-170?
b. Does HFD-170 have any specific requests regarding the electronic submission?
c. Does HFD-170 have any specific requests regarding the organization of the datasets?

d. Is HFD-170 in agreement with inclusion of 40-character, rather than 32-character, descriptive variables in the SAS datasets?

FDA RESPONSE:

- **The requirements for the Clinical Summary and Clinical Overview in the CTD do not supersede the regulations concerning the ISE and ISS. ISE and ISS should be prepared in conformance with U.S. regulations. These may be placed in the proposed CTD sections if they fit, or elsewhere if more convenient.**

- **All major components of safety and efficacy reviews should be placed together. Specifically, all the analysis, results, and discussion of the ISS should be in module 5, with only brief overviews and discussion in module 2. The same comments apply to the ISE.**

- **The overall design of the electronic submission and datasets should permit the reviewer to recreate all sponsor efficacy and safety results.**

Mr. Gensinger stated that the ISS and ISE belong in Section 5.3.5.3. while summary information belongs in Module 2. The Sponsor stated that they plan to submit the NDA in the traditional format with only Item 3 (clinical summary information) in CTD format. Mr. Gensinger clarified that the NDA will be filed electronically; documentation is prepared in Modules 1 through 5, but is filed in the traditional electronic-document folders. The Sponsor added that hyperlinks within the documents will allow easy navigation through the application. Dr. Rappaport reminded the Sponsor to test the application prior to submitting it. Mr. Gensinger suggested that if the Sponsor has any questions they could e-mail them to esub@cder.fda.gov.

- **All datasets should have a common unique patient identifier to permit merging datasets and/or tracking individual patients.**

- **Datasets should include adverse event (AE) preferred and verbatim terms, dates of onset and conclusion of AE, dose at onset of AE, duration on that dose, and duration and outcome of AE.**

- **SAS datasets must be submitted in Version 5 Transport format. Variable names or labels should therefore be capable of unambiguous representation in this format.**

- **The integrated summary of safety (ISS) should include specific sections addressing any safety problems found by DNDP and DRUDP during their respective NDA reviews.**

- **A compilation of all study sites should be included in the electronic submission. This information is not currently included within the CTD format.**

- **Provide patient profiles in ".PDF" format. Avoid ".PDX" format.**

Question 3: Does HFD-170 agree that our proposed plan to define databases will facilitate determination of safety of duloxetine for the treatment of DNP?

FDA RESPONSE:

- **The definitions of the safety databases are appropriate.**

The number of patient exposures appears grossly adequate, but adequate exposure at the highest doses must be provided.

The Sponsor stated that the open-label extension phase of the two studies to 120 mg will provide some data, but that most (approximately 50%) of the data being collected are at the 60-mg dose (target dose).

- **Provide CRFs and narratives for all deaths, SAEs and withdrawals due to AEs from all studies contributing to the safety database (i.e. completed & ongoing MDD, SUI, — and — -pain studies)**

The Sponsor stated that submitting ongoing data for discontinuations due to adverse events would be a problem since the databases will still be locked. The Division stated that all available CRFs and narratives for deaths and SAEs should be submitted for ongoing studies and all appropriate CRFs and narratives for completed studies. Studies completed during the review cycle should be submitted at the 120-day safety update.

Question 4: Does HFD-170 agree that if the outcomes of these two studies are positive, they will be sufficient to achieve an indication of efficacy of duloxetine in — 'DNP?

FDA RESPONSE:

- **The design of the two placebo-controlled trials (HMAW & HMAV) appears adequate to support efficacy.**

- **The efficacy outcomes and safety data will be taken into consideration in determining if duloxetine can be granted an indication for —**

Question 5: Does HFD-170 agree that the plans outlined in the meeting package adequately address the topics from the End of Phase II meeting?

FDA RESPONSE

- **Pharmacology/Toxicology: Reference to NDA 21-427 electronic submissions are acceptable. Cross linking and supporting literature references would be very much appreciated.**

- **Biopharmaceutics: The sponsor should conduct a study to evaluate the PK of duloxetine in patients with mild and moderate renal impairment.**

The Sponsor stated that they agreed with the Division's assessment of the limited utility of the population pharmacokinetic analysis in evaluation of the effect of renal impairment on duloxetine PK. They stated that they have evaluated data from patients with mild and moderate renal impairment using a traditional PK approach following the first clinical study. They plan to evaluate data from patients with mild and moderate renal impairment in a second clinical trial, as well. The Sponsor asked if this

information would be sufficient. Dr. Al-Fayoumi stated that it should be acceptable pending Agency review of the data. The Sponsor stated that the patients in the HMAV study were not distributed according to degree of renal impairment, so the Sponsor is evaluating creatinine levels, etc. to gather these data. Dr. Al-Fayoumi stated that the Division will review these data and discuss.

Dr. Al-Fayoumi stated that the Sponsor currently has pharmacokinetic data for patients with moderate hepatic impairment. He stated that this information is adequate provided that the Sponsor —— The Sponsor stated that they have to clarify this issue with Neuropharm because they feel that this wording is incorrect. The Sponsor intends to propose ——

Abuse Liability:

- **Reference to NDA 21-427 is acceptable.**
- **If abuse potential data is in the electronic NDA 21-427, a copy of this information should be submitted to HFD-170 for review.**

Question 6: Is the proposal to reference the — study reports in the MDD and SUI NDAs acceptable?

FDA RESPONSE

- **All CRFs and narratives are required for the 3 relevant categories (SAEs, discontinuations due to AEs, and deaths) for the — studies.**

The Sponsor stated that — owns the data and at this time it is unavailable for submission to the Division. The Sponsor asked whether they could submit particular listings based on review. Drs. Rappaport and Hertz stated that until the application is under review, they will not know which listings to request. Submitting requested reports during the review cycle will be problematic due to the shortened time restraints of a priority review. The Sponsor stated that they will work this out with —

Question 7: Does HFD-170 agree that the Request for Waiver of Studies in Pediatric Patients would be granted?

FDA RESPONSE

- **Provide data to support the request for a waiver.**

Question 8: Is HFD-170 in agreement that the content described within this briefing document, including the cross-referencing to — (for study reports only) and NDA 21-427, comprises a complete NDA and that, at this time, no issues are apparent that would result in a "Refusal to File?"

FDA RESPONSE
'Refuse to File' decisions can only be made after review of the submitted NDA.

The Sponsor asked if there are any issues in the current meeting package that appear to be problematic. Dr. Hertz stated that the Division had communicated all potential issues that were evident during review

of the meeting package during this meeting. She also reminded the Sponsor that there may be issues discovered during review of the submission that are not evident in the current meeting package.

Question 9: What is the Division's current assessment of the likelihood of a priority review?

FDA RESPONSE

- **A priority review will be granted for NDAs for products intended for the — as there are currently no products approved for this indication.**

Question 10: Please describe how your division will likely apply these concepts (CDER/CBER Risk Assessment Working Group - Good Risk Management Practices) in the review of new NDA submissions within the time frame of 2004-2005?

FDA RESPONSE

- **It is unlikely additional studies such as comparative safety studies, would be requested.**
- **Basic principles in this concept paper concerning adequate number of patients, exposure at higher doses, DDI, time of occurrence of AEs, and dose at occurrence of AEs are not novel.**

Additional Discussion:

Secondary Outcome Measures

The Sponsor stated that during evaluation of their data they discovered an interesting finding that they would like to discuss —

Dr. Hertz stated that the Sponsor should add this information to the draft labeling for review.

Special Vulnerabilities in Diabetics

The Sponsor asked if there were particular aspects of diabetes such as renal failure and neuropathy that the Division would like studied with extra vigilance. Dr. Hertz stated that the Sponsor should evaluate things that are clinically relevant to diabetics such as glucose control. Dr. Rappaport added that the Division will scrutinize the data with respect to these issues and also gave ophthalmic disease as another example.

Priority Review

The Sponsor stated that they will try to be responsive to the Division's needs noting that the Division will be under a tight time frame. Dr. Hertz stated that it is helpful to have complete datasets that contain the relevant information and that are hyperlinked and easily navigated. The Sponsor questioned if the 120-day due date is reduced for a priority review application. The Division stated that they were unsure and that they would find confirm this. **(After meeting note: The Division confirmed that the safety update for a priority review remains due at 120-days.)** The Division reminded the Sponsor that they prefer one, complete safety update rather than intermittent pieces of information as they become available. Dr. Hertz also stated that the Division evaluates all safety data from controlled

and open-label studies independently and combined together. The Sponsor stated that some Divisions do not evaluate data from studies not conducted in the US.

Timing of Submission

The Sponsor stated that they are ahead of schedule and plan to submit this application at the end of January 2004. The Sponsor questioned if an advisory committee would be utilized for this review. The Division stated that an advisory committee would only be assembled if it was necessary for a specific issue.

The Sponsor asked if the Division reviews the labeling in the last month of the review cycle. The Division confirmed that they typically do.

CTD Format

The Sponsor asked for clarification as to whether their proposed format and content of the submission was acceptable to the Division. Dr. Hertz stated that Item 8 should be in Module 5, not in Module 2. Mr. Gensinger added that the preparation and placement of information were two different items. He suggested that the Sponsor review the draft guidance carefully. The Sponsor clarified that only "executive summary" information would be in Module 2 while the full ISS and ISE would be in Module 5.

[redacted] indication

The Sponsor asked what the requirements were for a [redacted]

The meeting adjourned at 2:45 pm

Minutes prepared by: Lisa M. Malandro

{See appended electronic signature page}

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/s/

Lisa Malandro
8/26/03 06:07:43 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

EOP2 meeting minutes
9/23/02

IND 62,536

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Attention: Sharon Hoog, M.D.
Senior Regulatory Research Scientist
U.S. Regulatory Affairs-CNS

Dear Dr. Hoog:

Please refer to the meeting between representatives of your firm and FDA on August 8, 2002. The purpose of the meeting was to discuss the clinical development plan of duloxetine hydrochloride for

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7407.

Sincerely,

{See appended electronic signature page}

Lisa Marie Malandro
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Industry Meeting Minutes

Meeting Date: August 8, 2002 Time: 1:00 PM

Location: Parklawn Building, Conference Room C

Drug: Duloxetine (LY248686)

Sponsor: Eli Lilly and Company

Indication: Pain Disorders

Type of Meeting: End of Phase 2

Meeting Chair: Bob Rappaport, M.D., Deputy Division Director

Minutes Recorder: Lisa M. Malandro, Regulatory Project Manager

Eli Lilly Attendees	Title
Gregory T. Brophy, Ph.D.	Director, U.S.Regulatory Affairs
John R. Hayes, M.D.	Product Team Leader, Joint Antidepressant Group
Pierre Tran, M.D.	Medical Director, Duloxetine Product Team
Richard F. Bergstrom, Ph.D.	Research Advisor, Pharmacokinetics
Smriti Iyengar, Ph.D.	Senior Biologist, Neuroscience Research
Yili Lu, Ph.D.	Research Scientist, Statistics
Sharon L. Hoog, M.D.	Senior Research Scientist, U.S. Regulatory Affairs
FDA Attendees	Title
Cynthia McCormick, M.D.	Division Director
Bob Rappaport, M.D.	Deputy Division Director
Eric Duffy, Ph.D.	Director, DNDC II
Tim McGovern, Ph.D.	Team Leader, Pharmacology/Toxicology
Shaun Comfort, M.D.	Medical Officer
Ravi Harapanhalli, Ph.D.	CMC Reviewer
Dan Mellon, Ph.D.	Pharmacology/Toxicology Reviewer
Suliman Al-Fayoumi, Ph.D.	Biopharmaceutics Reviewer
Stella Grosser, Ph.D.	Statistics Reviewer
Katherine Bonson, Ph.D.	CSS Reviewer
Lisa Malandro	Regulatory Project Manager

Meeting Objective: The objective of the meeting was to discuss the clinical development plan of duloxetine hydrochloride for

General Discussion: Following introductions, the discussion focused on the sponsor's questions which were included in the July 3, 2002, meeting package. The sponsor's questions are listed in italics.

1. *Does the Division agree that two positive studies with duloxetine in the is sufficient for approval?*

FDA Response:

In principle the Agency agrees. However, several points must be emphasized:

- The studies must be Adequate and Well Controlled Clinical Trials of appropriate size.
- The two clinical trials must be of sufficient duration to meet regulatory requirements (≥ 12 weeks).
- The studies must meet their primary outcome measures.

2. *Does the Division agree that duloxetine may be considered for priority review?*

FDA Response:

This is acceptable for priority review based upon:

- There is no current "approved" therapy for this indication (PDN) (i.e., "Potential for significant advancement in treatment")
- The sponsor's Phase II data shows efficacy based upon the Phase II study (F1J-MC-HMAW) of 457 subjects showing a SSD between DLX 60 qD & BID vs. PBO with $p < 0.001$.

Discussion:

The Sponsor asked the Division how judgements are made about Advisory Committees. The Division stated that decisions are based upon difficult issues or specific questions. An Advisory Committee meeting would not be necessary for this drug unless there was a particular problem or issue. The Division stated that they make every attempt to issue approval letters during the first review cycle.

3. *Does the Division agree that the results of Study HMAW demonstrate that the analgesic effect of duloxetine is independent of its effect on mood?*

FDA Response:

No. The Agency is not persuaded that DLX pain-efficacy effects can be completely distinguished from concurrent effects on mood. (Refer to similar question in — Letter and Biostatistics reply)

However, in spite of this difficulty, this issue may be of lesser importance if the product produces a clinically relevant analgesic effect.

In the Phase 3 trials it is important to study patients as close to the "real world" population as possible. Therefore, we would encourage you not to exclude subjects with psychiatric diagnoses in these trials. Other methods could be included to assess for factors specifically attributable to this particular subgroup.

Discussion:

The Sponsor indicated that depression studies have included measures of pain, but not diabetic neuropathy. There was a significant effect on the pain component. The Division stated that they would be interested in seeing this information (secondary database). The Sponsor indicated that they will ask that the electronic NDA currently being reviewed in HFD-120 remain on the server so that this Division can access it.

The Division stated that they would like to see a broader patient population (i.e. "as close to real world") included in the Phase 3 trials. The Division suggested that the Sponsor broaden the entry criteria (i.e., do not exclude patients with psychiatric diagnosis) and compare the first and second trials. The Sponsor expressed their concern regarding previously treated and currently treated depression patients. The Division stated that randomization should eliminate some of those issues. The Division has concerns that the effect will be diluted out. The Sponsor questioned whether other FDA divisions dealing with pain medications also require a similar patient population. The Division stated that they did because they want to approve the drug for a target population.

4. *What methods would the Division consider acceptable if applied to the outcomes of the second protocol (HMAV), which would then* —

FDA Response:

The acceptability of — will be assessed during review.

Note that the Draft Guidance (Clinical Studies Section of Labeling for Prescription Drugs and Biologics-Content and Format, May 2001) states that "if two or more endpoints are closely related and convey essentially the same information, only one should be presented."

Examination of the endpoints to see which ones are closely related will be a matter for review.

Discussion:

The Sponsor inquired about the methods used to determine what is in a label. The Division stated that relevant secondary endpoints that address analgesics specifically are evaluated at the time of the NDA review. The Division stated, as an example, that unvalidated quality of life measures are not accepted. This can be discussed at a pre-NDA meeting. The Sponsor indicated that they had some study results that they feel will be helpful to prescribers. The Division stated that they would ask the Sponsor to suggest them and they would then be discussed. The Sponsor inquired if it would be helpful to the Division to have a global patient assessment. The Division said yes, but as a secondary endpoint.

5. *Lilly proposes that Phase 3 trials of duloxetine in patients with painful diabetic neuropathy do not need to evaluate doses less than 60 mg QD. Does the Division agree?*

FDA Response:

This proposal is acceptable to the agency.

6. *Does the Division agree that the proposed exposure package for duloxetine is sufficient for approval?*

FDA Response:

No, the Agency does not agree.

Although the 1-year exposure (≥ 100 subjects) is adequate, the 6-month exposure is not sufficient.

- There should be ≥ 1000 PDN subject exposures total.
- There should be larger numbers of PDN subjects at the 6 month point, typically ≥ 500 (up to 1000).
- The major depressive disorder (MDD) and stress urinary incontinence (SUI) safety database should be included with the peripheral diabetic neuropathy (PDN) NDA submission, as part of the global safety exposure.
- In addition to an ISS for the entire safety population, a separate analysis of the PDN safety database should also be performed.

Discussion:

The Division stated that if there are data for patients with diabetic neuropathy in the current NDA (being reviewed in HFD-120), it should be included in the NDA submitted to this Division. The Sponsor stated that they may have some, but that the patients may not have been diagnosed. The Sponsor asked if the data for the PDN should be presented alone as well as tabulated with the MDD/SUI data in a global database. The Division confirmed this and stated that they would like to see the MDD/SUI data even if it is not analyzed. The Division stated that it would also be nice to

see information about concomitant medications and disease progression. The Sponsor inquired if, in general, 300 patients was an insufficient amount of data or if it was just insufficient for this indication. The Division stated that since this is a fragile patient population that is generally older and the drug could potentially be used very widely, it is preferable to have as many patients as possible.

7. *Does the Division agree that the results from these assessments at 15 months in Study HMAW and at 3 months in Study HMAV are adequate and sufficient to show that duloxetine does not accelerate the progression of diabetic complications?*

FDA Response:

The Agency recommends performing nerve conduction velocities (NCVs) initially, and at appropriate times during the study (e.g.. middle, end):

- To insure that the disease severity is equally distributed across treatment groups (i.e. no bias)

- To insure that Duloxetine efficacy is not inadvertently due to subsequent worsening of the patient's nerve function.

Discussion:

The Sponsor requested more specific information regarding the NCVs (i.e., how many time points and what times are appropriate). The Division stated that patients should be screened prior to the study and 3 and 15 months following study initiation. Additionally, an efficacy evaluation should be performed at 3 months. The Sponsor inquired about how many patients should be included in the evaluations. The Division gave an example of possible sample size.

8. *For an NDA submission to HFD-170, Lilly intends to reference NDA 21-427, and submit only additional information that is generated subsequent to the depression NDA. Does the Division agree?*

FDA Response:

CMC Response:

Reference to NDA 21-427 is acceptable. However, the drug substance and drug product specifications will be evaluated from the point of dosing regimen for the new NDA. Similarly, any issues specific to the new NDA, if not covered by NDA 21-427, will have to be addressed.

Pharm/Tox Response:

The proposal appears acceptable.

- Metabolite differences are an issue of concern:
  - Quantitative analysis of circulating drug and metabolites in humans and animals in terms of AUC or steady state blood levels should be provided.
  - Demonstration of adequate qualification of major metabolites in all toxicology studies should be provided with the NDA.

Discussion:

The Sponsor asked which metabolites the Division considers major and which metabolites the Division would be most interested in. At this time, the Division stated that they are interested in the same four major metabolites identified in the NDA. The metabolites are: glucuronide conjugate of 4-hydroxy duloxetine, sulfate conjugate of 5-hydroxy 6-methoxy duloxetine, glucuronide conjugate of 6-hydroxy 5-methoxy duloxetine and glucuronide conjugate of dihydroxyl/catechol duloxetine. Of these four, three are not clearly found in the plasma of animals; and therefore data regarding their qualification will be required. The Division requests that a quantitative analysis of the human metabolites in terms of the AUC or steady state levels be provided. In addition, a quantitative analysis of the animal metabolites will be needed to assess adequate coverage of the human metabolites in the animal studies. Once that data is obtained, further qualification of human-specific metabolites may be needed.

The Sponsor inquired if a profile from other tissues could be presented to the Division if the metabolites are not found in animal plasma. The Division confirmed that metabolite data in other tissues may be used to predict exposure levels as part of a weight of evidence approach. However, the data should be presented in terms of predictions of human exposure to be able to predict toxicities.

The Sponsor inquired about acceptable procedures in the event that the metabolite(s) are not produced by animals. The Division stated that the metabolite(s) can be synthesized and tested in toxicology studies. The Division requested that data generated for the NDA being reviewed — HFD-120 be forwarded to HFD-170.

The Sponsor inquired if a decision made in — HFD-120 would be honored by HFD-170. The Division stated that they would collaborate with — and HFD-120, but that the risk benefit ratio may be different in each group. The Division stated that a major concern was carcinogenicity since this could be a potentially long-term treatment and the only treatment available to many patients.

BioPharm Response:

Reference to NDA 21-427 is acceptable. The sponsor needs to provide the following additional information:

- PK in various grades of renal & hepatic impairment
- Potential DDIs with likely-co-administered drugs (in particular, CYP 2D6 substrates)

Discussion:

The Sponsor expressed their concerns that a change observed at study end may be related to end-stage renal disease rather than the drug. Further, the Sponsor indicated that hepatic impairment in previous studies was clinically significant. They stated that duloxetine is a moderate CYP 2D6 inhibitor. The Sponsor gave a brief summary of what studies they had completed with CYP 2D6 substrates and inquired if what they had completed was sufficient. The Division stated that typical drugs administered for this patient population should be reviewed and any drugs that have been previously excluded should be included in Phase 3 trials. The Division stated that drugs to consider include antipsychotics, antidepressants, opioids and beta blockers. The Sponsor stated that they generally exclude opioids. The Division suggested that the Sponsor choose two or three drugs that are known to be substrates and evaluate them. Evaluation can be a sampling of an open label study or clinical trial. The Division agreed that the Sponsor may present an argument that evaluation of CYP 2D6 with model substrates may be adequate to address their concerns.

Abuse Liability Information:

Submit an Abuse Liability Package as part of the NDA (21 CFR § 314.50 (5) (vii))

- **Proposal for scheduling and all scientific data that forms the basis of the proposal**
- Abuse Liability assessment
  - Chemistry (Including chemical similarity to other drugs of known abuse potential)
  - Pharmacology (Clinical and pre-clinical)
    - Pharmacokinetics and pharmacodynamics
    - Integrated summary of Safety and Efficacy
    - Information related to overdose

Discussion:

The Sponsor agreed that duloxetine does not have abuse liability and plans to present a summary of data supporting this in the NDA. Electronic links to the pertinent information will be provided.

Additional Discussion:

1. The Sponsor inquired about the Division's feelings about path analysis. The Division stated that they are suspicious of this type of data analysis since it is very sensitive to early specifications. Some useful information may be obtained, but it should be a secondary analysis.

2. The Sponsor stated that the painful physical symptoms associated with depression are of particular interest to them.

3. There was a brief discussion regarding the use of electronic diaries.

4. There was a brief summary of the meeting.

The meeting adjourned at 2:30 pm

Minutes prepared by: Lisa M. Malandro

Minutes concurred by Chair: Bob Rappaport, M.D.

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/s/

Bob Rappaport
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