

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-148

PHARMACOLOGY REVIEW(S)



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

PHARMACOLOGY/TOXICOLOGY MEMO TO THE FILE

NDA NUMBER: 22-148
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 8/14/2007
PRODUCT: Duloxetine hydrochloride (Cymbalta®)
INTENDED CLINICAL POPULATION: Patients with fibromyalgia
SPONSOR: Eli Lilly and Company
DOCUMENTS REVIEWED: Electronic Submission: no nonclinical
data submitted
REVIEW DIVISION: Division of Anesthesia, Analgesia, and
Rheumatology Drug Products (HFD-170)
PHARM/TOX REVIEWER: Kathleen Young, Ph.D.
PHARM/TOX SUPERVISOR: Adam Wasserman, Ph.D.
DIVISION DIRECTOR: Bob Rappaport, M.D.
PROJECT MANAGER: Parinda Jani

Date of review submission to Division File System (DFS): April 25, 2008

EXECUTIVE SUMMARY

I. Recommendations

- A. **Recommendation on approvability:** This NDA can be approved from a Pharmacology and Toxicology perspective.
- B. **Recommendation for nonclinical studies:** None. The results of the nonclinical studies conducted under the referenced drug product (NDA 21-427, Cymbalta®, for the treatment of major depressive disorder and generalized anxiety disorder, Eli Lilly) and NDA 21-733 (Cymbalta®, for the treatment of diabetic peripheral neuropathic pain, Eli Lilly) were previously reviewed and found to support the safety and recommendation for approval from a pharmacology and toxicology perspective.
- C. **Recommendations on labeling:** None. The recommended revisions to the relevant nonclinical sections of the label were satisfactorily addressed for Cymbalta® under the referenced NDA # 21-427 and NDA # 21-733.

II. **Summary of nonclinical findings:** No new nonclinical studies were submitted for this NDA.

III. **Nonclinical safety issues relevant to clinical use:** None

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/s/

Kathleen Young
4/25/2008 01:48:04 PM
PHARMACOLOGIST
pharmacology and toxicology

Adam Wasserman
4/25/2008 01:52:11 PM
PHARMACOLOGIST
I concur.

PHARMACOLOGY/TOXICOLOGY NDA FILEABILITY CHECKLIST

Division of Anesthesia, Analgesia, and Rheumatology Products

NDA Number: 22-148

Applicant: Eli Lilly and Company

Stamp Date: August 14, 2007

Drug Name: CYMBALTA (LY248686, duloxetine hydrochloride)

IS THE PHARM/TOX SECTION OF THE APPLICATION FILEABLE? Yes [x] No []

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameters	Yes	No	Comment
1	On its face, is the Pharmacology/Toxicology section of the NDA organized in a manner to allow substantive review to begin?			NA: reference NDA 21-427 for the non-clinical pharmacology and toxicology information to support safety
2	Is the Pharmacology/Toxicology section of the NDA indexed and paginated in a manner to allow substantive review to begin?			NA
3	On its face, is the Pharmacology/Toxicology section of the NDA legible so that substantive review can begin?			NA
4	Are final reports of ALL required* and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility*, juvenile studies, ocular toxicity studies*, acute adult studies*, chronic adult studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)? Have electronic files of the carcinogenicity studies been submitted for statistical review?			NA
5	If the formulation to be marketed is different from that used in the toxicology studies, has the sponsor made an appropriate effort to either repeat the studies with the to be marketed product or to explain why such repetition should not be required?			NA: will use approved market formulation
6	Are the proposed labeling sections relative to pharmacology appropriate (including human dose multiples expressed in mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?	X		Labeling to be revised to comply with PLR format
7	For a 505(b)(2) submission, has the sponsor identified a referenced product?	X		
8	For a 505(b)(2) submission, has the sponsor submitted patent certification information to support the information referenced in the proposed drug product labeling?	X		
9	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions?			NA: no studies requested
10	Based upon a cursory review, do the excipients appear to have been adequately qualified?	X		
11	Has the applicant submitted any studies or data to address any impurity or extractable issues (if any)?			NA
12	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route?			NA
13	Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			NA
14	Has the sponsor submitted a statement(s) that the pharm/tox			NA

	studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?		
15	From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not.	X	FILING ISSUES:
16	If the NDA is fileable, are there any filing review issues that need to be conveyed to Sponsor? If so, specify:	X	Filing review issues for the 74-day letter:

Note: None

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/s/

Kathleen Young
10/3/2007 07:27:58 AM
PHARMACOLOGIST

Adam Wasserman
10/3/2007 01:53:58 PM
PHARMACOLOGIST