CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-733

CHEMISTRY REVIEW(S)

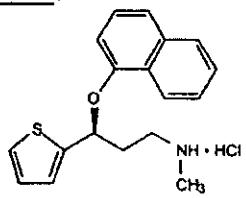
7/21/04

NDA REVIEW MEMO

NDA Number: 21-733

Applicant: Eli Lilly and Company
Indianapolis, IN 46285

Document date: 03/02/2004
Stamp Date: 03/03/2004
Drug Name: CYMBALTA (Duloxetine HCl)
Container Closure: — . Bottles/ — closures — . blisters
Strength/Dosage Form: 20, 30, 60 mg/Capsules, Delayed-Release
Route of Administration: Oral
Indication: —



Comments: (See Vol. 1.1, Note to Reviewer, p. 9)
The CMC section of this NDA is included by cross-reference to the CMC section for duloxetine HCl drug substance and drug product (capsules) provided in NDA 21-427 (CYMBALTA for the treatment of depression). HFD-120 is the lead reviewing division for CMC, as agreed in the pre-NDA meeting of 7/30/2003 with HFD-170. The CMC review in HFD-120 (four reviews, reviewers J. Christy and C. Tele) resulted in the resolution of all the CMC deficiencies in NDA 21-427 and the CMC recommendation for duloxetine HCl was for approval. Duloxetine HCl (proposed name: —

There were no CMC issues specific to the HFD-170 product. No new strengths are proposed. The same packaging and a common label (PI and container labels) have been proposed for the HFD-120 and HFD-170 products. Container labels have been provided for the 20, 30 and 60 mg capsules in HFD-170. Proposed treatment dose for DNP is the 60 mg, but the 20 and 30 mg strengths will be available as well.
We note, that duloxetine HCl (chemical structure shown above) is an NME and a novel serotonin and norepinephrine re-uptake inhibitor. It is synthesized as a single optical isomer (one chiral center) in the S-configuration. For drug substance specifications, see NDA 21-427 CMC Review #2. Retest date is not proposed, but the drug substance is stable fo under normal and accelerated conditions with some supportive long-term stability data of — . The drug substance is acid-labile, and the formulation is encapsulated enteric-coated pellets, for delayed release in the stomach (two hours). The finished enteric-coated pellets consist of a sugar sphere core — a duloxetine HCl layer, — , an enteric layer and a color layer. Additional excipients (capsules) are sucrose, hypromellose, talc, — — The capsule colors are distinct for the different strengths: 20 mg (opaque green/opaque green), 30 mg (opaque blue/opaque white), 60 mg (opaque blue/opaque green). For drug product specifications, see NDA 21-427 CMC Review #2. 24 months expiration dating was granted for the drug product in bottles and blisters (see NDA 21-427 CMC Review #2).
The following two Eli Lilly facilities perform all manufacturing, testing and packaging for duloxetine HCl:

1. Drug substance manufacturer:	2. Drug product manufacturer, packager, labeler
Eli Lilly Co./Tippecanoe	Eli Lilly and Co.
Box 685, Lilly Road	Lilly Corp. Ctr./White River Pky/East Dr.
Lafayette, IN 47902	Indianapolis, IN 46200

The overall OC recommendation is "ACCEPTABLE" as of 01/06/2004 (see NDA 21-427 CMC Review #4).

CONCLUSION/RECOMMENDATION: NDA 21-733 is recommended for approval for CMC based on the HFD-120 recommendation, with no specific issues related to the HFD-170 product.

Review Chemist: Danae Christodoulou, Ph.D. Date: 7/21/04
Team Leader: Ravi Harapanhalli, Ph.D. Date: 7/21/04

cc:
Original NDA 21-733
HFD-170/Division File
HFD-170/Chem/DChristodoulou
HFD-170/TL/RHarapanhalli
HFD-170/PM/LMalandro
HFD-820/DivDir/Chem/EDuffy

File: NDA21733REVIEW.DOC

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

/s/

Danae Christodoulou
7/21/04 05:35:37 PM
CHEMIST

Ravi Harapanhalli
7/21/04 05:48:37 PM
CHEMIST

NDA FILEABILITY CHECKLIST

NDA Number: 21-733

Applicant: Eli lilly and Company
Indianapolis, IN 46285

Stamp Date: 03/03/2004
Drug Name: CYMBALTA (Duloxetine HCl)
Container Closure: — Bottles/ , — closures/ —
Strength/Dosage Form: 20, 30 — 60 mg/Capsules, Delayed-Release
Route of Administration: Oral
Indication: —

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) Yes

Comments: (See Vol. 1.1, Note to Reviewer, p. 9)
The CMC section of this NDA is included by cross-reference to the CMC section for duloxetine HCl drug substance and drug product (capsules) provided in NDA 21-427 (CYMBALTA for the treatment of depression). HFD-120 is the lead reviewing division for CMC, as agreed at the pre-NDA meeting of 7/30/2003 with HFD-170. After 4 rounds of CMC review in HFD-120, all the CMC deficiencies in NDA 21-427 had been resolved and the CMC recommendation for Duloxetine HCl was for approvable action.

Based on the NDA 21-427 CMC reviews, this application meets filing requirements. No CMC issues specific to the HFD-170 product have been indicated at this point. Any further CMC and labeling issues specific for NDA 21-733 will be addressed as needed during the review cycle.

Review Chemist: Danae Christodoulou Date: 5/10/04
Team Leader: Ravi Harapanhalli Date: 5/10/04

cc:
Original NDA 21-733
HFD-170/Division File
HFD-170/Chem/DChristodoulou
HFD-170/TL/RHarapanhalli
HFD-170/PM/LMalandro
HFD-820/DivDir/Chem/EDuffy

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

/s/

Danae Christodoulou
5/10/04 04:33:18 PM
CHEMIST

Please e-sign

Ravi Harapanhalli
5/10/04 06:07:41 PM
CHEMIST