CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 721-427

Administrative/Correspondence #2

MEMORANDUM

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

DATE: October 16, 2003

FROM: Director, Office of Drug Evaluation I, HFD-101

SUBJECT: Approvable action on duloxetine (Cymbalta, NDA 21-427, Eli Lilly)

TO: File, NDA 21-427

Most issues are fully covered in summarizing memos of Drs. Katz and Andreason, but I have a few comments.

1. Dose

The sponsor has no data directly comparing daily doses of 80-120 mg with lower (40-60 mg) doses, as discussed by Dr. Andreason, and cross-study comparisons cannot provide valid comparisons. In the absence of such evidence and given that most safety data reflect the lower doses, I see no reason to even hint in labeling that higher doses be tried, specifically by noting that higher doses are effective (of course they are; how many umbrella shaped D/R studies are there?).

2. Liver

Dr. Racoosin's review concludes, correctly, I think, that there are no clear "Hy's rule" cases. There does seem to be a small, but real, increase in the rate of 3x transaminase elevations, so that a very few such cases would be a significant concern, but I find none persuasive, including patient 500-5254 (Lilly identifies as a Hy's Rule case), whose picture was clearly obstructive, with a huge elevation of AP. Patient A09505 also had an obstructive component and a suggestion of xs ethanol use, while E00301 never had elevated transaminases. Patient A06706 also had a clear obstructive component present at baseline. A305-3512 has, as Dr. Racoosin notes, an odd time course. The placebo cases don't look like much either. Although it is possible duloxetine plus alcohol is a problem, it is very hard to know, in an alcoholic, whether LFT abnormalities are the result solely of the alcohol or are related to the alcohol-duloxetine combination.

All in all, the cases (5 on duloxetine, 2 on placebo) include, in my view, no smoking guns. It is of interest, however, that review of recent psychotropic agents showed no Hy's Law cases, but I don't think the duloxetine cases are Hy's Law cases either, as in such cases there is not supposed to be 1) baseline abnormality or 2) evidence of much obstruction (AP can go up a little), which all had. I think proposed labeling has it about right. This could turn out to be a problem but with very substantial exposure (n=8000) in trials (not Clin Pharm short term) there are no very good cases and in about one-fourth the exposure to placebo, there are 2 cases about as good as most of the duloxetine cases; the latter finding seems pertinent to the result of our review of other drugs. (Once we have full data on the 2 placebo cases and 5th duloxetine case, we may need to modify labeling to reflect those cases.)

Table 1
Duloxetine Cases

Case	Problem/Comment
E00301	No real TA elevation
A09505	Very high TA but substantial increase in AP and very rapid TA recovery
500-5254	10X TA elevation but huge increase AP and elevated bilirubin persisted well after TA normal. Also, well-documented binge drinking and chronic liver disease.
A06706	Clear obstructive component and drinking history, improvement while on drug
305-3512	Rapid (one day) decrease in TA (single elevated value) is odd but hard to think TA, AP, GCT, and bili all represent lab error.

3. QT

Despite the QT concept paper's urging that essentially all drugs have a "thorough" QT assessment including an active control (this and other aspects of the concept paper are under very active discussion), the available data base on duloxetine looks very benign with respect to QT. Dose matters, of course, and patients with inhibited 2D6 and 1AZ pathways could leave exposures at least 8 times the uninhibited exposure (5X for 1AZ, about 1.5X by 2D6 inhibtion); this should be formally studied.

The recommended daily dose of duloxetine is 60 mg. There are studies of 160-240 mg per day, representing exposures of 3-4 times the recommended exposure, with no signal of prolongation up to 200 mg/day and probably nothing at 240 mg/day, although as Dr. Racoosin points out, there is some ambiguity here. As she notes, and despite our efforts to develop more formal QT assessment, clinical studies have readily found QT prolongations of even 10 msec (the results of clinical studies and a formal QT study with ziprasidone were very similar, and detected a modest [10-12 msec] effect).

Robert Temple, M.D.

cc:
HFD-101/R Temple
draft:sb/9/29/03;9/30/03
final:sb/10/16/03
filename:duloxetine_MM_Sep03.doc

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/s/

Robert Temple
10/16/03 07:31:55 PM
MEDICAL OFFICER

M E M O R A N D U M

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

DATE: September 17, 2003

FROM: Paul J. Andreason, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for Duloxetine in the Treatment of Major Depressive Disorder

TO: File, NDA 21-427
[Note: This memo should be filed with the original March 24, 2003 complete response to Approvable Action submission of this NDA.]

1.0 Background

This memo is a Team Leader summary and recommendation for a second Approvable Action on NDA 21-427, Duloxetine for the Treatment of Major Depressive Disorder. The sponsor submitted a complete response to the Division's first Approvable Action letter on September 13, 2002. Since the sponsor's original submission time they completed two additional studies in Major Depressive Disorder and submitted — for Duloxetine for the Treatment of Stress Urinary Incontinence (SUI). During the review — and since the Division's Approvable Action of September 13, 2002, three new cases of liver toxicity were reported. These cases were reviewed by Zili Li, MD of the Division of Reproductive and Urological Drug Products (DRUDP), John Senior, MD, and by Judy Racoosin, MD, the Division's Safety Team Leader.

[ ]

2.0 Chemistry

NDA 21-427 for Cymbalta® (duloxetine hydrochloride) is recommended for **NOT APPROVABLE** from the Chemistry, Manufacturing and Control standpoint because the Office of Compliance has recommended a **WITHHOLD APPROVAL**. This recommendation is based on significant cGMP violations at the finished product manufacturing facility Eli Lilly and Co., Indianapolis (CFN 1819470). The future potential approval shall be based on an overall acceptable cGMP recommendation from the Office of Compliance for all manufacturing, packaging, labeling, and testing facilities. All other CMC concerns related to the drug substance and drug product sections as outlined in the Chemistry review of the original NDA by Dr. Christy John have been addressed in the Complete Response to Approvable Action Letter.

3.0 Pharmacology/Toxicology

The Pharmacology/Toxicology issues that precluded approval of this NDA have been resolved to the satisfaction of the Pharmacology Toxicology Review Team. Adequate information was submitted to

allow qualification of the impurities [ ], whose specifications have been set at — for the clinical batches, an amount that is above the threshold for qualification.

The Pharm-Tox Reviewer was Linda Fossom, PhD. She notes that the labeling calculations implying human pharm-tox safety margins used a human weight of kg as a basis for the estimate in lieu of the usual 60-kg standard. Dr. Fossom recommends changing the labeling to correct for this discrepancy.

4.0 Biopharmaceutics

Office of Biopharmaceutics and Clinical Pharmacology (OCPB) found that the Sponsor's reply was acceptable for approval from an OCPB standpoint.

The sponsor agreed to perform the previously requested Phase IV commitment within 3 months of approval (assuming approval on this review cycle). This commitment includes two *in vitro* dissolution experiments examining the stability of the enteric coating by examining the extent of naphthol formation. The first experiment examines stability [ ] The second experiment examines stability [ ] The sponsor has specified that naphthol formation will be quantified utilizing an analytic method using 1-naphthol as reference standard and the results will be reported as the percentage of labeled duloxetine. This commitment is acceptable to OCPB with the modification that the amount of 1-naphthol generated should also be reported, in addition to reporting it as a percentage of labeled duloxetine.

5.0 Clinical Data

Efficacy

The Division's original labeling did not recommend doses above 60-mg/day. The Sponsor presented the results of one positive study that supports doses of up to 60-mg BID as effective. Study HMAYa was a non-US, 9-week double blind, placebo and active controlled, fixed dose and parallel group study of duloxetine 40 and 60-mg BID versus placebo and paroxetine 20-mg/day. The primary efficacy variable was the change in baseline to endpoint of the HAM-D 17 total score using an ITT LOCF analysis. Patients treated with duloxetine in both patient treatment groups (40 and 60-mg BID) had statistically significantly greater improvement at the endpoint in the primary efficacy measure (HAM-D17 total score) compared with placebo-treated patients in both repeated measures analysis and endpoint LOCF analysis. Thus, there is now evidence that doses of 80 and 120-mg/day divided BID are effective.

The following table is reproduced from the statistical review by Dr. Ohidul Siddiqui. Study HMAYb (referred to in the table footnote below as Study B) was identical to HMAYa but failed.

Mean Change from Baseline to Endpoint (end of week 9) STUDY HMAYa

		LOCF ANCOVA analysis				Repeated Measure analysis			
TRT (N)		LS Mean change [1]	P-values			LS Mean change [1]	P-values		
			Vs. 1	Vs. 2	Vs. 3		Vs. 1	Vs. 2	Vs. 3
1)	Placebo (N=93)	-8.07				-8.78			
2)	Dulox40BID (N=95)	-10.22	**.007**			-11.01	**.001**		
3)	Dulox60BID (N=93)	-11.06	**<.001**	.297		-12.08	**<.001**	.122	
4)	PRX20QD (N=86)	-10.83	**.001**	.458	.784	-11.68	**<.001**	.347	.569

[1] Ls mean change from baseline.
LOCF model: In Study A: PROC GLM Model= Trtmnt, Poolinv, and Baseline for Main Effects p- values.
LOCF model: In Study B: PROC GLM Model= Trtmnt, Poolinv, Baseline and Trtmnt* Poolinv for Main Effects p-values.
Repeated Analysis Model: In both studies: Model hamd17= Therapy visit poolinv Therapy* visit basval basval* visit; Cov. Unstructured

The sponsor also argues that 60-mg/day is the optimal dose and they wish to delete the reference in labeling [redacted] as being effective. There is no one study that compares all of the doses head to head. The sponsor argues that there are two studies where 60-mg QD were positive and only one of two studies showed that doses as low as 20-mg BID were effective. The sponsor uses a cross-study comparison of effect size to support the argument that 40-mg/day is too low of a target dose. While effect sizes were generally greater at higher doses, the U.S studies' effect sizes are smaller as compared to the effect sizes in the non-U.S study. There fore the comparison in effect sizes may not be valid in this case. On a study by study basis, there is as much evidence to suggest that 40-mg/day is effective as there are positive studies to suggest that up to 120-mg/day is effective (one positive study to support each dose claim). I therefore recommend [redacted]

Safety
There are two areas of concern with respect to duloxetine safety that are new since the first action was taken in September of 2002, potential liver toxicity and concern over the lack of higher human plasma exposure data with respect to QTc. Both of these issues are comprehensively reviewed by Judy Racoosin, MD, the safety Team Leader.

Potential for Hepatotoxicity
There are several partial reviews on this subject that are presented during this review cycle. Dr. Glass the primary reviewer for duloxetine requested Safety Team Consultation and though she recommends [redacted], this was a provisional recommendation that was made due to time constraints without the benefit of Dr. Racoosin's report. Dr. Zili Li of HFD-580 reviewed three liver toxicity cases in the SUI development program but did not discuss the two placebo treated patients with elevated transaminase. Dr. Racoosin also includes a review of the most recent report of a woman in South America with elevated transaminases that conceivably resolved even though she apparently continued on drug (if the history can be trusted). This single additional case was also reviewed by John Senior, MD.

Dr. Racoosin also audited three previously submitted NDAs to sample for rates of reported hepatotoxicity associated with ethanol use during drug development. She found that in her sample of recently approved NDAs that there were no cases of severe liver toxicity that were attributed to heavy ethanol use. Hence, I consider Dr. Racoosin's review on the subject of hepatotoxicity and duloxetine the definitive review to this date. Drs. Li, Glass, and Senior make recommendations based on a less complete benefit of the accumulated data. She concludes and recommends the following with respect to liver toxicity with which I concur.

> "Duloxetine can cause hepatotoxicity in the form of transaminase elevations. It may also be a factor in causing more severe liver injury, but there are no cases in the NDA database that clearly demonstrate this. Use of duloxetine in the presence of ethanol may potentiate the deleterious effect of ethanol on the liver.
>
> 1. Placement of a Precautions statement describing the transaminase abnormalities and cases of severe liver injury associated with the combination of duloxetine use and ethanol abuse
> 2. Request that the sponsor provide close monitoring of the postmarketing experience of duloxetine with regard to liver AEs
>   a. Sponsor will be asked to expedite reporting of all liver-related Aes received during the postmarketing period
>   b. Sponsor will be strongly encouraged to provide extensive detailed follow-up on reported cases; cases that are poorly documented will be considered related to the drug until the sponsor shows otherwise
>   c. Sponsor will be asked to provide quarterly summaries on all liver related Aes along with an estimate of drug usage for that quarter and an explanation of the method used to estimate drug usage
>   d. DNDP, along with the Office of Drug Safety, will review the submitted data
> 3. In the event that unconfounded cases of severe liver injury or acute liver failure related to duloxetine treatment are identified and submitted early in the postmarketing period, the division will use the threshold of three "clean" cases to initiate additional regulatory action that could range from a more prominent warning to the withdrawal of the drug product."

Potential for QTc Prolongation

I was the primary reviewer for duloxetine for its initial submission. Since that time there have been no cases of death or serious adverse events due to arrhythmias. There have likewise been no cases of discontinuation for clinically significant elevation of QTc. In the clinical trial database there were no trends for increases in QTc either in mean values or outlier analysis. Reviewers in DRUDP concur on this issue. Their point of concern is that with the inhibition of two cytochrome P450 metabolic pathways (1A2 and 2D6) patients might be exposed to more than the equivalent of 240-mg/day.

It is conceivable that patients taking duloxetine might also be augmented with sertraline or paroxetine (CYP2D6 inhibitors) and a fluoroquinolone antibiotic or fluvoxamine (CYP1A2 inhibitors). Though this could conceivably occur, it would probably be in a very small number of patients. The lack of any finding in clinical studies to date gives some reassurance that even if the combination treatment that I described did occur, there would be little or no effect.

I think that it is important that we ultimately know the effects of optimal inhibition on plasma kinetics and QTc; however, given the lack of a signal in all studies to date and the relatively lower risk of maximal inhibition in the depressed population, I concur with Dr. Racoosin that this is a study that could be deferred to a phase IV commitment.

Monitoring for Hypertension
The routine monitoring of blood pressure was recommended in the first review cycle. The Sponsor argues that monitoring for hypertension is not necessary. I continue to disagree. There is an adequate signal to recommend routine monitoring for hypertension. This recommendation is also present for venlafaxine that has a similar pharmacologic mechanism of action. There was a dose dependant increase in the number of patients that had one or more blood pressure readings that were higher than 140/90. Since labeling will now recommend doses up to 120-mg a day (where 24% of patients had one or more readings of 140/90 vs. 9% of placebo patients) it is more than reasonable to monitor blood pressure routinely.

It is fairly clear that there is not any indication that duloxetine may place patients at risk for the kind of malignant hypertension that is seen with the MAOI antidepressants. Nonetheless, duloxetine is a drug that if effective will be used for periods of 6-months to several years. Chronic mild hypertension is a quiet painless condition that can not be detected without monitoring. Chronic hypertension is connected with long-term mortality and morbidity.

The Sponsor argues that there was not a signal for sustained hypertension (i.e. multiple sequential readings of elevated blood pressure) and in the limited population for the limited amount of time that the drug has been studied under placebo controlled conditions, this is true. My counter-argument is that the studies were not large enough or long enough to make a judgment about the true risk of sustained hypertension. Until such time as a study of patients with borderline hypertension can be done it is prudent to suggest monitoring given the present signal and I stand by my previous recommendation for routine monitoring.

6.0 WORLD LITERATURE
Dr. Glass reviewed 28 articles and abstracts submitted as part of the safety update. She reports that there were no new safety findings in these articles and abstracts.

7.0 FOREIGN REGULATORY ACTIONS
To my knowledge, duloxetine is not approved in any country at this time.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING
We decided not to take this NDA to the PDAC.

9.0 DSI INSPECTIONS
No additional DSI inspections were requested for this review cycle.

10.0 LABELING AND APPROVABLE LETTER
10.1 Draft of Labeling Attached to Approvable Package
Our proposed draft of labeling is attached to the approvable letter. As noted, we have made changes to the sponsor's draft labeling.
10.2 Foreign Labeling

Duloxetine is not approved for the treatment of MDD anywhere at this time.

10.3 Approvable Letter

The approvable letter includes draft labeling and requests for phase IV commitments, safety update, a literature update and a regulatory status update.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I recommend that the Division take a second Approvable Action (AE) on duloxetine for the treatment of Major Depressive Disorder. This recommendation is based on CMC deficiencies outlined in section 2.0 of this memo.

Future potential approval of duloxetine for the treatment of Major Depressive Disorder should be based on at least the following:

1. An overall acceptable cGMP recommendation from the Office of Compliance for all manufacturing, packaging, labeling, and testing facilities applicable to duloxetine

2. The sponsor agreed to perform includes two *in vitro* dissolution experiments examining the stability of the enteric coating by examining the extent of naphthol formation within three months of approval as a phase IV commitment. The first experiment examines stability after [ ] The second experiment examines stability [ ] The sponsor has specified that naphthol formation will be quantified utilizing an analytic method using 1-naphthol as reference standard and the results will be reported as the percentage of labeled duloxetine. This commitment is acceptable to OCPB with the modification that the amount of 1-naphthol generated should also be reported, in addition to reporting it as a percentage of labeled duloxetine.

3. The sponsor must agree to submit expedited reports for all liver-related adverse events received during the postmarketing period. Any potential case reports should provide extensive detailed follow-up; cases that are poorly documented will be considered related to the drug until the sponsor shows otherwise. Additionally, the Sponsor shall agree to provide quarterly summaries on all liver related adverse events along with an estimate of drug usage for that quarter and an explanation of the method used to estimate drug usage.

4. As a phase IV commitment we request that the Sponsor Conduct a prospectively designed study to evaluate the effect of duloxetine on the QT interval. This study should characterize the duloxetine plasma concentration-response relationship for QTc interval prolongation and evaluate the degree of QTc prolongation at plasma concentrations achieved following maximal potential interaction between duloxetine and the combination of CYP1A2 and 2D6 inhibitors. The QT study should be randomized and double-blinded and include both a placebo control and a positive control. We recommend that that the Sponsor submit their proposed plan and protocol for meeting this objective so that all Divisions (including DNDP, Divisions of Reproductive and Urologic Drug Products (DRUDP) and Cardio-Renal Drug Products (DCRDP)) can assess the acceptability of the protocol to fulfill their multiple requirements.

   Performance of a maximal inhibition study in older women [ ] I think that it is important that we ultimately know the effects of optimal inhibition on plasma kinetics and QTc; however, given the lack of a QTc prolongation signal in all studies to date and the

relatively lower risk of maximal inhibition in the depressed population, I concur with Dr. Racoosin that this is a study that could be deferred to a phase IV commitment for the purposes of DNDP.

5. Acceptable product labeling.

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/s/

Paul Andreason
9/17/03 02:27:37 PM
MEDICAL OFFICER

Office of Drug Safety

MEMO

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

From: Jinhee L. Jahng, 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

Jerry Phillips, R.Ph.
Associate Director, Office of Drug Safety
HFD-400

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

Date: June 20, 2003

Re: ODS Consult 01-0167-1, Cymbalta (Duloxetine Hydrochloride Capsules) 20 mg, 30 mg, 60 mg; NDA 21-427.

This memorandum is in response to an April 15, 2003 request from your Division for a re-review of the proprietary name, Cymbalta. The blister label, container label, carton and insert labels were provided for review and comment. The proposed proprietary name was found acceptable by DMETS on September 13, 2002 (ODS Consult # 01-0167).

Since that review, DMETS has identified one additional proprietary name, [redacted]**, as having the potential to sound similar to Cymbalta. [redacted]

Although [redacted] and Cymbalta share the same beginning sounds, [redacted] vs. "Cymb", the remaining portions of the name, [redacted]" vs. [redacted]", are different both phonetically and orthographically. [redacted]

[redacted] Cymbalta is a single ingredient (duloxetine) drug product indicated for major depressive disorder and will be available in strengths of 20 mg, 30 mg, [redacted] 60 mg. The dosage strengths do not overlap, however, [redacted] be available as oral capsules for once daily administration. Additionally, [redacted] Cymbalta are sponsored by the same manufacturer, Eli Lilly, and may be launched into the marketplace during the same time period. Confusion may be further compounded as a result of similarities in the active ingredients [redacted] Therefore, DMETS recommends that efforts be made to differentiate the packaging in hopes of minimizing the likelihood of possible confusion. In addition, DMETS would like to recommend that some educational measures be taken to emphasize the differences between these two medications at the time of approval.

In reviewing the container label, carton and insert labeling for Cymbalta, DMETS has identified some areas of possible improvement in the interest of minimizing potential user error.

A. BLISTER LABEL (20 mg, 30 mg, [redacted] 60 mg)

1. Please increase the prominence of the proprietary name and rearrange the information on the label so that the proprietary name appears at the top of the label. Once the lot number and expiration date are stamped onto the label, the proprietary name is negligible in appearance and it is indistinguishable from the other typed information.

2. Include the dosage form "capsule" in the established name.

B. INSERT LABELING

We noted that the initial daily dose is 60 mg and 30 mg daily in hepatic or renally impaired patients. However, Cymbalta will also be available as a 20 mg capsule. The insert does not contain information explaining when a dose of 20 mg is appropriate. Please justify the use of the 20 mg capsule.

In summary, DMETS has no objection to the use of the proprietary name provided the sponsor institutes an educational campaign that will ensure practitioner and patients know the differences of [redacted] Cymbalta. We also recommend revising the labels and labeling as outlined above. 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.

** This review contains proprietary and confidential information that should not be released to the public.

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/s/

Jinhee Jahng
7/9/03 09:28:24 AM
PHARMACIST

Alina Mahmud
7/9/03 09:34:48 AM
PHARMACIST

Carol Holquist
7/9/03 09:39:35 AM
PHARMACIST

Jerry Phillips
7/9/03 09:54:45 AM
DIRECTOR

MEMORANDUM

To: File, NDA 21-427

Through: Robert Temple, M.D., ODE I Office Director
Russell Katz, M.D., Division Director, Neuropharmacologic Drug Products
Barry Rosloff, Ph.D., Pharmacology Supervisor, HFD-120
Linda Fossom, Ph.D., Pharmacology Reviewer, HFD-120
Doris Bates, Ph.D., Regulatory Project Manager, HFD-120

From: Jeri El-Hage, Ph.D., ODE I Associate Director for Pharmacology/Toxicology

Subject: NDA 21-4274 , Duloxetine HCl, Cymbalta™
Tertiary Review of Pharmacology/Toxicology Data

Date: September 9, 2002

A complete toxicological evaluation of duloxetine HCl has been conducted and the toxicity profile supports the approvable recommendation of the pharmacology reviewer, Dr Fossum, and supervisor, Dr Rosloff. I concur with the recommendations of the supervisory pharmacologist that further preclinical safety evaluations of the conjugated metabolites, 4 hydroxy-duloxetine glucuronide and 5-hydroxy, 6-methoxy- duloxetine sulfate are not necessary based on the data and scientific rationale provided (see supervisory memo dated 9/4/2002). In addition, I also concur that based on a weight of evidence approach and the demonstrated absence of genotoxic potential in 5 different assays, repetition of the chromosomal aberrations assay in Chinese hamster ovary cells is not warranted.

The Division has requested that the sponsor provide data to demonstrate that the impurities [ ] were present in drug substance lots utilized in the pivotal toxicology studies or somehow otherwise comply with ICH Q3A (i.e., lower specification limits to < 0.1% or conduct additional preclinical studies, as appropriate). The nonclinical pharmacology/toxicology section of the approvable letter on page 3 is acceptable, as written.

The preclinical sections of the labeling in the approvable letter (pp 11-12) are also acceptable.

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/s/

Jeri El Hage
9/12/02 01:57:40 PM
PHARMACOLOGIST

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: July 24, 2001	**DUE DATE:** September 13, 2002	**ODS CONSULT #:** 01-0167

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

THROUGH: Doris Bates
Project Manager
HFD-120

PRODUCT NAME: **Cymbalta** (Duloxetine Hydrochloride Capsules) 20 mg, 30 mg, 60 mg **NDA #: 21-427**	**NDA SPONSOR:** Eli Lilly and Company

SAFETY EVALUATOR: Tia M. Harper-Velazquez, Pharm.D.

SUMMARY: In response to a consult from the Division of Neuropharmacological Drug Products (HFD-120), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Cymbalta" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION: DMETS has no objections to the use of the proprietary name, Cymbalta.

The firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names or established names from the signature date of this document.

Carol Holquist, R.Ph.
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-5161

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: July 12, 2002

NDA# 21-427

NAME OF DRUG: **Cymbalta**
(Duloxetine Hydrochloride Capsules)
20 mg, 30 mg, 60 mg

NDA HOLDER: Eli Lilly and Company

I. INTRODUCTION:

This consult is written in response to a request from the Division of Neuropharmacological Drug Products (HFD-120), for an assessment of the proposed proprietary name, Cymbalta. The container labels, carton and insert labeling for Cymbalta were reviewed for possible interventions in minimizing medication errors. Additionally the sponsor submitted an independent analysis of the name for review and comment. This analysis was conducted by [redacted]

PRODUCT INFORMATION

Cymbalta contains duloxetine hydrochloride and is indicated for the treatment of depression. The recommended dose of Cymbalta is one capsule once or twice daily with or without food, based on response and tolerability. It will be available in strengths of 20 mg, 30 mg, 60 mg capsules.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound alike or look alike to a degree where potential confusion between drug names could occur under the usual

[1]MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.
[4]WWW location http://www.uspto.gov/tmdb/index.html.
[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[4] and the Saegis[5] Pharma-In-Use database were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Cymbalta. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified three proprietary names that were thought to have the potential for confusion with Cymbalta. These products are listed in table 1 (below), along with the usual dosage and available dosage forms.

2. DDMAC did not have concerns about the name Cymbalta with regard to promotional claims.

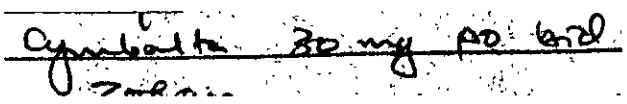
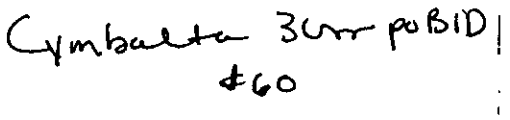
Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	**Dosage form(s), Established name**	**Usual adult dose***	**Other****
Cymbalta	**Duloxetine Hydrochloride Capsules 20 mg, 30 mg, 40 mg, and 60 mg**	**Take orally, once or twice daily depending on response and tolerability. May be taken with or without food.**	
Tagamet	Cimetidine Tablets 200 mg, 300 mg, 400mg, and 800 mg	Active duodenal ulcer: 800 mg at bedtime for 4-8 weeks. Maintenance 400 mg at bedtime. Active benign gastric ulcer: 800 mg at bedtime or 300 mg 4 times daily with meals and at bedtime for 6 weeks. GERD: 800 mg 2 times daily or 400 mg 4 times daily for a maximum of 12 weeks.	SA/LA
Symmetrel	Amantadine Hydrochloride Tablets: 100mg, Syrup 50mg/5mL	200 mg taken daily in one or two divided doses. Dose is reduced in patients with renal dysfunction.	SA
Cinobac	Cinoxin Capsules 250 mg and 500 mg	1 gram daily, administered orally in 2 or 4 divided doses (500 mg twice a day or 250 mg four times a day) for 7 to 14 days. Dose is reduced in renally impaired patients.	SA/LA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Cymbalta with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 109 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Cymbalta (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

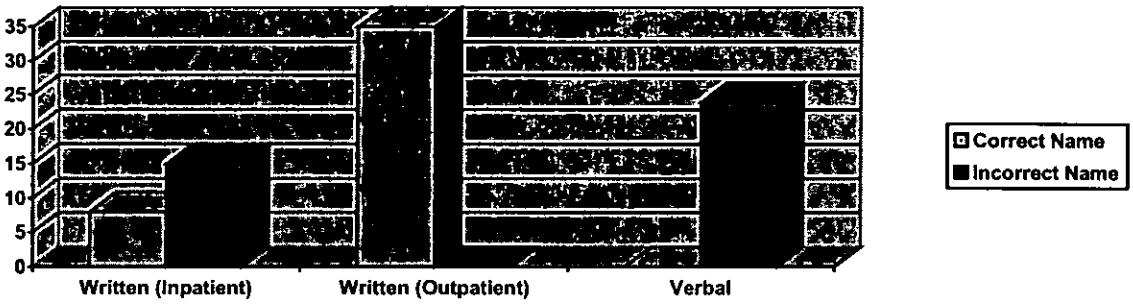
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: 	Cymbalta 30mg by mouth twice a day, #60.
Inpatient RX: 	

2. Results:

The results are summarized in Table 2.

Table 2

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	35	23 (66%)	8 (35%)	15 (65%)
Written Outpatient	39	35 (90%)	35 (100%)	0 (0%)
Verbal	35	24 (69%)	0 (0%)	24 (100%)
Total	109	82 (75%)	43 (52%)	39 (48%)



Among the verbal prescription study participants for Cymbalta, 24 of 24 (100%) of the participants interpreted the name incorrectly. The majority of the incorrect name interpretations were phonetic variations of "Cymbalta." The incorrect responses were *Symbalta (5), Simbolta (5), Zimbalta (4), Simbalta (3), Sambalta (1), Simbalka (1), Simbaltra (1), Simbata (1), Symbolka (1), Symboltra (1), and Zembolta (1).*

Among the written prescription study participants for Cymbalta, 15 of 58 (26%) participants interpreted the name incorrectly. The majority of the responses were misspelled variations of "Cymbalta", however in one case the incorrectly interpreted name was Cyanocobalamin, a marketed drug name. Other incorrect responses were *Cynbalta (2), Cynbaltin (1), Cymoloatan (1), Cymboltin (1), Cymbolta (1), Cymbalton (1), Cymbalter (1), Cymbaltar (1), Ceprabalta (1), Apubalta (1), Cyanbalta (1), Cyanobak (1), and Cyanobalton (1).*

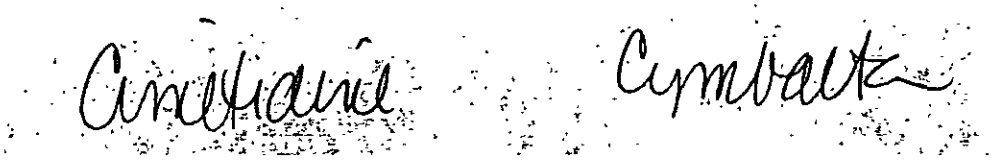
C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Cymbalta", the primary concerns raised were related to three look-alike and/or sound-alike names: Cimetidine, Symmetrel, and Cinobac.

We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between Cymbalta and Cimetidine, Symmetrel, or Cinobac. The majority of the incorrect interpretations of the written and verbal studies were misspelled/phonetic variations of the proposed name, Cymbalta. However, a negative finding does not discount the potential for name confusion given the limited predictive value of these studies, primarily due to the sample size.

Cimetidine (generic Tagamet) is an H_2-blocker, indicated for the treatment of active duodenal or benign gastric ulcers, maintenance of healed duodenal ulcers, and the treatment of gastroesophageal reflux disease (GERD). The DMETS Expert Panel expressed concern that the proposed name, Cymbalta, looks and sounds similar to Cimetidine as they share the same phonetic prefix ("cim" vs. "cym"). The beginning of each word ("cimet" vs "cymb") may look alike depending upon how they are scripted (see page 6). However, the endings of each word ("dine" vs. "balta") are clearly different in look and sound. Depending on the indication, Cimetidine and Cymbalta may share overlapping dosing intervals (twice daily). The strengths contain overlapping numerals (200 mg, 300 mg, and 400 mg vs. 20 mg, 30 mg, , which may be confused if Cymbalta is written with a trailing zero and an undistinguished decimal point. However, the difference in spelling and sound of the drug endings may help to decrease the potential risk of medication errors between Cimetidine and Cymbalta.

Cimetidine **Cymbalta**



Symmetrel is the proprietary name for Amantadine. Symmetrel is a prescription-only product indicated for the prophylaxis and treatment of signs and symptoms of infection caused by various strains of influenza A virus. It is also indicated in the treatment of Parkinson's disease. Symmetrel is available as a 100 mg tablet and a syrup with a concentration of 50 mg/5 mL. The DMETS Expert Panel expressed concern that Symmetrel and the proposed name, Cymbalta, sound similar as they share the same phonetic beginning ("sym" vs. "cym"). The remaining syllables ('metrel" vs. "balta") do not sound alike. The drugs also differ in dosage form and dosage strength. Symmetrel is available in 100 mg tablets and 50 mg/5 mL syrup, whereas Cymbalta is available in 20 mg, 30 mg, 60 mg capsules. Additionally, Symmetrel and Cymbalta will not be stored near each other on pharmacy shelves. Although both drugs may be given twice daily, overall the differences should reduce the risk of confusion between the products.

Cinobac is a prescription-only medication indicated for the treatment of initial and recurrent urinary tract infections in adults. The DMETS Expert Panel expressed concern that Cinobac and the proposed name, Cymbalta, may sound and look similar. The beginnings of the names are phonetically similar ("cin" vs. "cym"), and may look alike when scripted (see below). However, the endings of each name ("obac" vs. "balta") are different and therefore reduce the Cinobac and Cymbalta look-alike and sound-alike characteristics. Additionally, the medications differ greatly in strength and dosage regimen. Cinobac is available in strengths of 250 mg and 500 mg, whereas Cymbalta is available in strengths of 20 mg, 30 mg, 60 mg. The initial dose for Cinobac is 1 gram daily, administered orally in 2 or 4 divided doses for 7 to 14 days, whereas Cymbalta is give once or twice daily depending on response and tolerability. Given the differences in strengths and dosing regimen with a lack of convincing look-alike potential, the risk of confusion between the products is minimal.

Cinobac **Cymbalta**

Additionally, one respondent in the written study misinterpreted the inpatient prescription as Cyanocobalamin, a vitamin B12 supplement. Cyanocobalamin is available over the counter in strengths of 100 mcg, 500 mcg, 1000 mcg, and 5000 mcg tablets. It is also available in a prescription injectable form in a strength of 1,000 mcg/mL. Although Cyanocobalamin and Cymbalta share similar alphabetical characters, the ending letters of each name ("anocobalamin" vs. "mbalta") clearly distinguishes the names from each other (see page 7). Both drugs are available in oral dosage forms, however since the oral form of Cyanocobalamin is available over the counter, this reduces potential confusion between the two products. Cyanocobalamin and

Cymbalta do not have overlapping prescription dosage forms or strengths (1,000 mcg/mL injection vs. 20 mg, 30 mg, 60 mg capsules). Given these differences, the risk of confusion between the products is minimal.

Cyanocobalamin	Cymbalta
Cyanocobalamin	Cymbalta

D. STUDY SUBMITTED BY APPLICANT

At the request of Eli Lilly and Co., [ ], "evaluated the trademark candidate Cymbalta to determine its potential for medication errors due to look-alike or sound-alike confusion with other medications." Practitioners identified as likely to use the product in their practice settings performed [ ] assessment for Cymbalta. Practitioners were asked to script Cymbalta, and respondents, which included pharmacists from the United States, France, and Germany, reviewed the handwritten samples of the trademark, and pronounced it according to pronunciation guidelines. The respondents took into consideration factors such as drug procurement, storage, dispensing, handling, administration, as well as the patient population. Data was assembled for analysis using a combination of Internet, email, and faxes.

Two names, not considered in this review were identified by — as having possible look-alike similarity to Cymbalta. These products are Cisplatin (United States), and Cymevan (France). The — assessment stated that due to the different routes of administration and dosing schedules, the chance of actual confusion between Cisplatin and Cymbalta is very unlikely. Additionally, the difference in dosing and dosage schedule reduces the chance confusion between Cymevan and Cymbalta.

— provided the following conclusion statement in regard to the proposed name, Cymbalta:

> "After a careful review of all available data, it appears that Cymbalta should be able to co-exist in the markets that were tested with reasonable assurance that it will not create confusion that could lead to medication errors."

We agree with the conclusion provided by — . that Cymbalta should not pose a significant safety risk. Cisplatin can look and sound similar to Cymbalta because they share similar letter combinations ("ci" vs. "cy"). However they differ in dosage form, strength, and dosing regimen. Cisplatin is supplied as an injectable solution with a concentration of 1 mg/mL. Cymbalta, on the other hand will be available as a capsule in strengths of 20 mg, 30 mg, 60 mg. The products also differ in dosing regimen. Cisplatin is administered by intravenous infusion over 6 to 8 hours, whereas Cymbalta is taken once or twice daily. Furthermore, Cisplatin must be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents, while Cymbalta is used mainly in an outpatient setting. Given the differences in dosage form, strength, and dosing

regimen, the risk of confusion between Cisplatin and Cymbalta is minimal. Although Cymevan and Cymbalta share the same prefix ("cym" vs. "cym), the ending letters of each name ("evan" vs. "balta") distinguishes the names from each other. Additionally, Cymevan is marketed in France, and would therefore cause minimal confusion with products in the U.S. market.

IV. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels and carton labeling of Cymbalta, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified several areas of possible improvement, which might minimize potential user error.

A. BLISTER LABEL

1. Ensure the lot number is included on each individual Identi-dose blister label.
2.
3. Include the dosage form "capsule" in the established name.

B. BLISTER CARTON LABELING

1. See comment A-1.
2. Include the dosage form "capsules" in the established name.
3. Include an "Each capsule contains (insert appropriate number) mg of duloxetine hydrochloride" statement.
4. The font size of the printed material is too small. Increase font size by relocating the logo or decreasing the logo in size.

C. CONTAINER LABEL

1. See comment under BLISTER CARTON.
2. The expression of strength for the 20 mg container label (1000 capsules) is missing from the sample provided.
3. The Poison Prevention Act required the use of a child-resistant closure (CRC) cap on unit-of-use drug products. We note you propose to market Cymbalta in unit-of-use bottles containing 30, 60, and 90 tablets. Ensure the use of a child-resistant closure.

D. INSERT LABELING

1. The print is too small and therefore illegible. Please revise.
2. We noted that the initial daily dose is 60 mg and 30 mg daily in hepatic or renally impaired patients. However, Cymbalta will also be available as a 20 mg capsule. The insert does not contain information explaining when a dose of 20 mg is appropriate. Please justify the use of the 20 mg capsule.

V. RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name Cymbalta.

2. DMETS recommends implementation of the labeling revisions as outlined in Section IV of this review.

This decision is considered a tentative. The firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names from this date forward.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

/s/

Tia M. Harper-Velazquez, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
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Concur:

/s/

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
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/s/

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Carol Holquist
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PHARMACIST

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