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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-427

Pharmacology Review(s)

PHARMACOLOGY/TOXICOLOGY MEMO TO THE FILE

NDA 21-427.
Submission N-000, BZ; stamp-dated 12/22/03.

Drug: duloxetine HCl.
Sponsor: Eli Lilly and Company.
Indication: Major Depressive Disorder.

Reviewer: Linda H. Fossom, Ph.D., Pharmacologist
HFD-120.

RE: The Sponsor's Complete Response to the 2nd Approvable Letter dated 9/29/03.

1 A SUMMARY OF THE PHARMACOLOGY/TOXICOLOGY ISSUES:

The Pharmacology/Toxicology issues that contributed to the Approvable decision, rather than Approval, for this NDA during the first review cycle were adequately addressed in the second review cycle. No Pharmacology/Toxicology issues were communicated in the second Approvable Letter (9/29/03) and no Pharmacology/Toxicology information was submitted in the Complete Response that is currently under review. However, in the current submission, the Sponsor has proposed changes to Pharmacology/Toxicology sections of the FDA DRAFT APPROVABLE LABELING that was provided in the second Approvable Letter and the acceptability of these proposed changes is addressed here.

2 BACKGROUND:

This NDA was originally submitted on 11/13/01, for the use of duloxetine HCl in the treatment of Major Depressive Disorder in adults. An initial Approvable Letter issued on 9/13/02, with several Chemistry, Biopharmaceutics, Pharmacology/Toxicology, and Clinical issues. A Complete Response to the (initial) Approvable Letter was received by the Agency on 3/15/03; the Pharmacology/Toxicology issues that precluded the approval of this NDA were adequately addressed in that submission (Pharmacology/Toxicology review dated 9/8/03). A second Approvable Letter issued on 9/29/03. The only issue relevant for Pharmacology/Toxicology in this second letter was the wording for labeling, particularly that for the Carcinogenicity and Reproductive Toxicology sections. That letter contained the FDA DRAFT APPROVABLE LABELING for those sections, including safety margins based upon a maximum recommended human dose (MRHD) of 60 mg per day and an (conservatively) estimated adult human weight of 60 kg (i.e., 134 lbs).

The current submission (dated 12/22/03) contains the Sponsor's Complete Response to the second Approvable Letter. There were no Pharmacology/Toxicology issues communicated in that letter and no Pharmacology/Toxicology information provided in this submission. However, the Sponsor has provided revised labeling, in which "Lilly has accepted many of [FDA's] proposals and made some counter-proposals for labeling language."

3 THE SPONSOR'S PROPOSED REVISIONS TO PHARMACOLOGY/TOXICOLOGY SECTIONS OF FDA DRAFT APPROVABLE LABELING:

3.1 CLINICAL PHARMACOLOGY/Pharmcodynamics:

The Sponsor proposes to describe duloxetine's affinity at the dopamine reuptake transporter as "less potent" rather than '[illegible]' based upon "actual data, derived from both microdialysis studies and receptor affinity studies (see Nonclin Pharm 10, submitted in NDA 21-427)."

The FDA DRAFT APPROVABLE LABELING for this section was: "Although the mechanism of the antidepressant action of duloxetine in humans is unknown, it is believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS. Preclinical studies have shown that duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a [illegible] inhibitor of dopamine reuptake. Duloxetine has no significant affinity for dopaminergic, adrenergic, cholinergic or histaminergic receptors *in vitro*. Duloxetine does not inhibit monoamine oxidase (MAO). Duloxetine undergoes extensive metabolism, but the major circulating metabolites have not been shown to contribute significantly to the pharmacologic activity of duloxetine. "

According to the studies in the original submission (as described in the P/T review), Ki's for *in vitro* binding were determined for duloxetine at cloned human monoamine reuptake transporters: Ki =0.8 nM at hSERT, Ki =7.5 nM at hNET, and Ki = 240 nM at hDAT. Similar binding affinities were determined for rat transporters: Ki = 0.5 nM at rSERT and Ki = 3.6 nM at rNET [data not provided on rDAT] and for inhibition of reuptake of monoamines into synaptosomes from rat brain areas: Ki = 4.6 nM for 5-HT (rat cerebral cortex), Ki = 16 nM for NE (rat hypothalamus) and Ki = 369 nM for DA (rat striatum).

The designation "no significant affinity" was used in labeling for receptors whose Ki's were > 1000nM.

3.2 PRECAUTIONS/Carcinogenesis, Mutagenesis, Impairment of Fertility and PRECAUTIONS/Pregnancy:

The Sponsor proposes that the MRHD is [redacted] mg per day and has calculated safety margins for animal studies based upon the [redacted] dose in humans, rather than the MRHD of 60 mg recommended by the Agency in the 2nd Approvable Letter (dated 9/29/03). Additionally, it appears that the Sponsor has calculated the safety margins based upon a human body weight of [redacted] kg, rather than the 60-kg adult weight used by the Agency. (See the FDA DRAFT APPROVABLE LABELING from the 2nd Approvable Letter (dated 9/29/03) and the revised labeling currently proposed by the Sponsor, which are both provided in the Appendix of this review.)

3.3 The Sponsor did not propose any changes to the following Pharmacology/Toxicology wording for labeling:

PRECAUTIONS/Nursing Mothers: The Sponsor accepted the wording from the FDA DRAFT APPROVABLE LABELING from the 2nd Approvable Letter (dated 9/29/03): "Duloxetine and/or its metabolites are excreted into the milk of lactating rats. It is unknown whether or not duloxetine and/or its metabolites are excreted into human milk, but nursing while on duloxetine is not recommended."

DRUG ABUSE AND DEPENDENCE/Physical and Psychological Dependence: The Sponsor accepted the wording from the FDA DRAFT APPROVABLE LABELING from the 2nd Approvable Letter (dated 9/29/03): "In animal studies, duloxetine did not demonstrate barbiturate-like (depressant) abuse potential. In drug dependence studies, duloxetine did not demonstrate dependence-producing potential in rats.

While duloxetine has not been systematically studied in humans for its potential for abuse, ..."

4 CONCLUSIONS:

The Pharmacology/Toxicology issues that prevented approval of this NDA were resolved by the Sponsor's response to the initial Approvable Letter (issued 9/13/02). In the 2nd Approvable Letter (issued 9/29/03), there were no Pharmacology/Toxicology issues, however, that letter provided FDA DRAFT APPROVABLE LABELING, which included wording for labeling for the Pharmacology/Toxicology sections where safety margins in reproductive toxicology and carcinogenicity sections were based upon a maximum recommended human dose (MRHD) of[ ] mg per day and a human body weight of 60 kg. In the current submission the Sponsor has generally accepted our recommended wording for the Pharmacology/Toxicology sections of labeling, with some important exceptions.

The safety margins in the labeling currently proposed by the Sponsor are based upon a MRHD of[ ] mg per day and apparently assume a human weight of [ ]g. At this time it is not clear whether the MRHD will be [ ] mg per day. Additionally, we routinely base safety margins on a 60-kg human.

The Sponsor also proposes to describe duloxetine's action at the dopamine reuptake transporter as "less potent" than its action at the serotonin and norepinephrine reuptake transporters, rather than describing its action as [ ]" as was proposed by the Agency and had been previously accepted by the Sponsor. In the original submission for this NDA, the Sponsor provided binding affinities for duloxetine at cloned human transporters for each of the monoamines: the Ki for hDAT was 240 nM, for hNET =7.5nM, and for hSERT= 0.8nM. Duloxetine's affinity was highest for the SERT; its affinity was 9-fold lower for NET and 300-fold lower for DAT. Since sites with Ki's ≥ 1000 nM were considered to have "no significant affinity," duloxetine's Ki of 240 nM for the human DAT can best be described as [ ] and "less potent" seems misleading.

It should also be noted that the labeling (from current electronic PDR) for several reuptake inhibitors (Celexa, Effexor, Paxil, and Zoloft) uses wording like "minimal effects," "weak inhibitors," and "only very weak effects" to describe affinities for other transporters that had ~2000-fold (Ki), 13-fold (IC50), 320-fold (Ki), and 20-fold (IC50) lower affinities, respectively (for inhibition of uptake of 3H- labeled monoamines in *in vitro* rat synaptosomal preparations; as described in the original NDA review for each drug). [The labeling for Prozac says that it was "...a much more potent uptake inhibitor of serotonin than of norepinephrine," and dopamine uptake was not mentioned, although (IC50) affinities were 25-fold and 21-fold for NE and DA, respectively, compared with 5-HT.]

5 RECOMMENDATIONS:

From a Pharmacology/Toxicology perspective, there are no issues that would prevent the approval of this NDA.

However, the wording for the Pharmacology/Toxicology sections of labeling should include safety margins for the reproductive toxicology and carcinogenicity studies that are based upon the maximum recommended human dose (MRHD) that is accepted by the Agency (presumably either 60 or [illegible] mg per day) and a human body weight of [illegible] kg, not [illegible] kg, as was used by the Sponsor in their proposed revisions of the FDA DRAFT APPROVABLE LABELING from the 2nd Approvable Letter (dated 9/29/03). Wording for labeling for these sections, with safety margins calculated for MRHD of 60 mg and for MRHD of [illegible] mg, has been previously provided in the Pharmacology/Toxicology Review of the Sponsor's response to the 1st Approvable Letter (Sponsor's response dated 3/24/03; review dated 9/9/03) and has been appended to this review.

Additionally, the Sponsor's proposed change in wording for the Pharmacodynamics section (i.e., changing the descriptor of duloxetine's action at the dopamine reuptake transporter to "less potent") is not acceptable and the Agency's proposed wording ([illegible]) should be retained.

Linda H. Fossom, Ph.D., Pharmacologist *{see appended electronic signature page}*
Lois Freed, Ph.D., Supervisor *{see appended electronic signature page}*

Cc:

APPEARS THIS WAY
ON ORIGINAL

6 APPENDIX

6.1 Labeling issues

With regard to labeling, the safety ratios (presented in the sections on "Carcinogenesis, Mutagenesis, Impairment of Fertility" and "Pregnancy") should reflect the MRHD accepted by the Agency and be calculated using a human body weight of 60 kg (see below).

Table showing values calculated for doses in terms of mg/m^2 and safety ratios for MRHDs of 60 mg per day.

SPECIES	DOSE		SAFETY RATIO	
	mg/kg *	mg/m^2 **	60-mg MRHD	MRHD
Human	(60mg→) 1	37		
	→) 2	74		
Mouse	50	150	4.1	2.0
	100	300	8.1	4.1
	140	420	11.4	5.7
Rat	10	60	1.6	0.8
	27	162	4.4	2.2
	30	180	4.9	2.4
	36	216	5.8	2.9
	45	270	7.3	3.6
Rabbit	10	120	3.2	1.6
	45	540	14.6	7.3

* Mg/kg doses in humans were calculated by dividing the daily dose in mg (i.e., 60 mg) by 60 kg, the average human body weight used by the Agency.
**Doses were converted from mg/kg to mg/m^2 by multiplying by 37, 3, 6, and 12 in humans, mice, rats, and rabbits, respectively.

4. pages redacted from this section of the approval package consisted of draft labeling

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/s/

Linda Fossom
6/28/04 11:36:17 AM
PHARMACOLOGIST

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7/1/04 04:03:38 PM
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