CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18-936/S-060/S-062/S-063

MEDICAL REVIEW(S)

APR 26 2000

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 18-936
SPONSOR: LILLY
DRUG: PROZAC (FLUOXETINE)
MATERIAL SUBMITTED: LABELING SUPPLEMENT REGARDING SEROTONIN SYNDROME (SLR-060)
DATE SUBMITTED: 7/6/99
DATE RECEIVED: 7/7/99

This supplement proposes [redacted] In 1998, The Netherlands Regulatory Agency requested Lilly to add serotonin syndrome to the Prozac labeling, prompting the sponsor to propose a similar change in this submission.

Current labeling-Contraindications

Monoamine Oxidase Inhibitors --There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving fluoxetine in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, Prozac should not be used in combination with an MAOI, or within a minimum of 14 days of discontining therapy with an MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks (perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses [*See* Accumulation and Slow Elimination *under* Clinical Pharmacology]) should be allowed after stopping Prozac before starting an MAOI.

Proposed Labeling-Contraindications (additions in bold)
Monoamine Oxidase Inhibitors - [redacted] there have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma). [redacted]

Therefore, Prozac should not be used in combination with an MAOI, or within a minimum of 14 days of discontining therapy with an

MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks (perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses [*See* Accumulation and Slow Elimination *under* Clinical Pharmacology]) should be allowed after stopping Prozac before starting an MAOI.

Also, in the "Other Events..." listing under Adverse Reactions, neuroleptic malignant syndrome is currently listed as a "rare" event. Lilly would like to add a footnote stating, "***Neuroleptic malignant syndrome is the COSTART term which best captures serotonin syndrome.**"

Finally, under Postintroduction Reports, Lilly would like to

"serotonin syndrome (a range of signs and symptoms that can rarely, in its most severe form, resemble neuroleptic malignant syndrome)"

Rationale for these changes

Lilly points out that SS and NMS can be distinguished. Briefly, the criteria for SS proposed by Sternbach in 1991 (Sternbach H., Am J Psychiatry 1991;48:705-713) were 3 or more of the following: altered mental status, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, fever. These should occur with use of a serotonergic drug and in the absence of other etiologies such as infections or neuroleptic drug use. In addition to discontinuation of the suspected drug, some clinicians treat SS with cyproheptadine, methysergide, or propranolol. In contrast, Lilly feels NMS is best characterized as a syndrome involving fever, rigidity, altered conciousness, tachycardia, labile blood pressure, and often leukocytosis and elevated CPK. NMS is more often fatal than SS, according to Lilly, except when SS results from combination of an SSRI and MAOI. Clinicians may choose to treat NMS with dopamine agonists. In sum, Lilly feels the two syndromes are clinically distinct, and may be managed differently. Presently, however, the COSTART thesaurus of adverse events recognizes NMS only, and thus SS is typically "coded" as NMS in COSTART.

In support of the proposed labeling, Lilly provided results from a search of their adverse event reporting database. Briefly, their search strategy was as follows. They searched for cases having at least 3 of the signs and symptoms of SS noted above, and for reports in which the term "serotonin syndrome" appeared in the text. However, they did not search for adverse events coded as NMS (even though that appears to be the appropriate coding for SS in the current version of COSTART). They also performed a Medline literature search for "fluoxetine" plus "serotonin syndrome."

This search yielded 245 case reports. Of these, 88 were specifically reported to be cases of serotonin syndrome. Lilly excluded 111 reports of the 245, for various reasons such as confounding variables, not reported by a health care professional, and so forth. Seven cases were excluded because they were diagnosed as NMS (although they did have the signs and symptoms of SS as well).

Of the 87 cases Lilly considered to be bona fide SS, 26 involved concomitant MAOIs, 12 involved concomitant lithium, and 31 involved no serotonergic concomitant medication. Of the latter 31 cases, 2 patients died within several weeks of the event.

Conclusions and Recommendations:

I agree that SS and NMS can resemble each other. With respect to rewriting the contraindication for MAOIs, however, I do not feel Lilly has fully justified their new labeling. It would be more to the point, I believe, for Lilly to retrieve the reports involving an MAOI combined with fluoxetine, and then review these cases to see how they can best be described; i.e., as cases of SS, NMS, or something different.

In the "Other Events..." table, I have no objection to adding the footnote as shown above.

With respect to the proposed changes to Postintroduction Reports, I would favor simply adding "serotonin syndrome" and retaining "neuroleptic malignant syndrome like events." As Lilly pointed out, NMS and SS can sometimes be distinguished, so I do not see _____ in this subsection.

I would recommend approval of the supplement only with these changes, unless Lilly can provide further supporting evidence and rationale.

4/25/00

Andrew Mosholder, M.D.
Medical Officer, HFD-120

NDA 18-9367
Div file
HFD-120 Laughren, David, Mosholder, Dubitsky

4-26-00

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APR 20 2000

REVIEW AND EVALUATION OF CLINICAL DATA

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4/20/00

Andrew Mosholder, M.D.
Medical Officer, HFD-120

NDA 18-9367
Div file
HFD-120 Laughren, David, Mosholder, Dubitsky

OCT 13 2000

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 18-936
SPONSOR: LILLY
DRUG: FLUOXETINE HYDROCHLORIDE (PROZAC)
MATERIAL SUBMITTED: SLR-062 LABELING SUPPLEMENT
DATE SUBMITTED: 8/22/00
DATE RECEIVED: 8/23/00

The purpose of this labeling supplement is to harmonize the Prozac labeling with the recently approved labeling for Sarafem, the fluoxetine drug product for the treatment of PMDD. In the cover letter, Lilly states that this supplement incorporates several pending supplements for Prozac.

Many of the changes are of a minor editorial nature, and I will not list them here. My only comment on the editorial changes concerns two proposed abbreviations. I do not believe it is desirable to use the abbreviations TCA and OCD universally, after only a single use of the complete phrases they represent in the Clinical Pharmacology section. In Lilly's proposal these abbreviations appear throughout the labeling, often very far from the one place where the abbreviations are explained. Although psychiatrists would be familiar with these abbreviations, that may not be the case for other health care professionals. However, I note that these changes have already been made in the Sarafem labeling.

The more substantive changes are the following:

1. Thioridazine contraindication: This supplement adds the contraindication for concomitant thioridazine that is included in the approved Sarafem labeling. The changes appear in Contraindications, Warnings and Precautions.

2. Under Warnings/Rash and Possibly Allergic Events, the adverse event terms laryngospasm and lupus-like syndrome have been added to the description of the clinical manifestations. This was requested in our letter of 6/7/00. These changes were added to the Sarafem labeling by Lilly in a "changes being effected" supplement (SLR-063, submitted 8/31/00).

3. Under Drug Interactions, the adverse reaction following concomitant sumatriptan has been added, as it appears in the approved Sarafem labeling.

4. Under Adverse Reactions, "Male and female sexual dysfunction with SSRIs" has been added. The language appears to be based upon that requested in the approvable letter for Sarafem, dated 12/22/99. The final version for Sarafem differs in that it appropriately omits discussion of male sexual dysfuntion. I note that this paragraph is missing the comments about anorgasmia that appear in the Sarafem label. Mention of priapism has been added, with the statement "Priapism has been reported with all SSRIs." This is irrelevant to Sarafem, of course, but is appropriate for Prozac. Also, I suggest restoring the term "psychiatric disorder" as we originally proposed in the Sarafem approvable letter, in place of "mood-related disorder."

5. Under Postintroduction Reports, the adverse event terms cataract, hypoglycemia, optic neuritis, pulmonary hypertension, and ventricular tachycardia/torsades de pointes have been added. Of these, cataract, hypoglycemia, and optic neuritis were added to the Sarafem

labeling in the 8/31/00 "changes being effected" supplement, while pulmonary hypertension and ventricular tachycardia/torsades de pointes were added at the time of Sararem's approval.

6. Under Overdosage, the Human Experience subsection has been completely revised. The language corresponds to that agreed upon in our letter dated 6/7/00. This revision was made to the Sarafem labeling with the 8/31/00 "changes being effected" supplement.

7. Under How Supplied, the instruction "Protect from light" has been added for all strengths of the "pulvules." This statememt was added in the Sarafem approval letter.

Conclusions and recommendations: I have only one suggested change, for the Sexual Dysfunction paragraph that is added under Adverse Reactions. I recommend that this paragraph include a statement similar to the one in the Sarafem label regarding orgasmic dysfunction. Here is my suggested sentence: "There have been spontaneous reports in women taking fluoxetine of orgasmic dysfunction, including anorgasmia." Also, in the Sexual Dysfunction paragraph, it might be desirable to replace the phrase "mood-related disorder," which was felt to be more appropriate for the PMDD population, with the more general term "psychiatric disorder: "Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a ~~mood-related~~ psychiatric disorder..."

With these changes, I recommend approval of this supplement. I suggest that we attempt to reach agreement with the sponsor, so that Lilly may submit the changes as "changes being effected."

10/12/00

Andrew Mosholder, M.D.
Medical Officer, HFD-120

NDA 18-936 SLR 062
Div file
HFD-120 Laughren, David, Dubitsky, Molchan, Bates, Mosholder

10-13-00