CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18-936/S-052
20-101/S-024

MEDICAL REVIEW

REVIEW AND EVALUATION OF CLINICAL DATA

NDA: 18-936/S-052 ; 20-701/S-024
SPONSOR: Eli Lilly and Company
DRUG: Fluoxetine HCl (Prozac) capsules
MATERIAL SUBMITTED: Geriatric Labeling Supplement
DATE SUBMITTED: 5/11/98
DATE RECEIVED: 5/12/98
MEDICAL OFFICER: Andrew Mosholder, M.D.

1. Background

This is Lilly's submission for Prozac pursuant to the Final Rule dated 8/27/97 requesting geriatric use labeling supplements from sponsors of marketed drugs. The current Prozac labeling includes description of data from two efficacy trials in depressed patients aged 60 years and older. Pharmacokinetic data is also included for patients aged 60 years and older. Since the Final Rule defines geriatric patients as those 65 years old or older, Lilly has performed subgroup analyses on these previously submitted data sets to examine the findings specifically for the subgroup of patients 65 years and older; i.e., excluding patients aged 60-64 from the data.

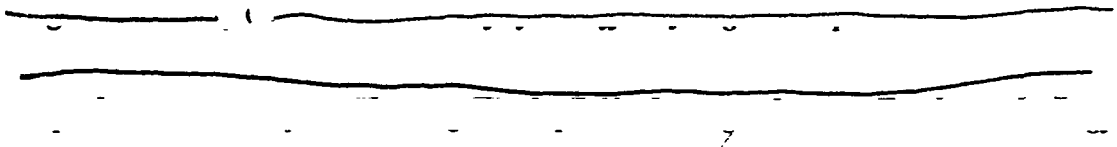
The sponsor's proposed labeling for this supplement includes the following changes (shown in bolded italic font).

Under Clinical Pharmacology
Age: The disposition of single doses of fluoxetine in healthy elderly subjects (> 65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half life and nonlinear disposition of the drug, a single dose study is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple drugs for concomitant diseases. The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (≥ 60 years of age) who received 20 mg fluoxetine for six weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 209.3 plus ± 85.7 ng/ml at the end of six weeks. No unusual age associated pattern of adverse events was observed in those elderly patients.

Under clinical trials:

Two six week controlled studies ***(n=671 randomized)*** comparing Prozac, 20 mg, and placebo have shown Prozac, 20 mg daily, to be effective in the treatment of elderly patients (≥ 60 years of age) with depression. In these studies, Prozac produced a significantly higher rate of response and remission as defined respectively by a 50 percent decrease in the HAMD score and a total endpoint HAMD score of ≤ *8*. Prozac was well tolerated and the rate of treatment discontinuations due to adverse events did not differ between Prozac (12 percent) and placebo (9 percent).

Under Precautions:



The above are the most substantive labeling revisions. There are a variety of other minor editorial changes to the labeling as well, such as changing "usage in the elderly" to "geriatric use" as specified in the Final Rule, and correction of some typographical errors. There is also a reference to hyponatremia that has been added under Geriatric Use. I will not list all of these here, for the sake of brevity; the complete set of Lilly's proposed labeling changes is attached to this review.

This submission contains a re-analysis of safety and efficacy data for two studies conducted under a single protocol, HCFF. The re-analysis excludes subjects aged 60 through 64 years. These re-analyses, according to Lilly, support the additional statements about geriatric patients shown above. Additional information included in this supplement comes from postmarketing experience with geriatric patients and a literature search.

Protocols HCFF Original Analysis:

I will here summarize briefly the results from the studies which are currently noted in the Prozac labeling, prior to presenting the results of the sponsor's reanalysis.

The two studies conducted under this single protocol were double blind, placebo controlled, randomized, parallel group studies. The purpose of these studies was to determine the safety and efficacy of fluoxetine 20 mg daily in treating major depressive disorder in geriatric patients. After a one week placebo washout period, subjects began six weeks of double blind treatment with fluoxetine 20 mg/d or placebo. The patients were male or female outpatients, 60 years of age or older, with major depressive disorder. A Hamilton Depression (HAMD) rating score of at least 16 on the first 17 items was required. Patients were to be medically stable, and without serious suicide risk.

A total of 860 patients entered the single blind placebo phase, and of these, 671 were found eligible for randomization. A total of 335 patients were randomized in study 1, and 336 in study two. Study one and Study two both had 15 sites. In study 1, 78 percent of the fluoxetine patients and 84 percent of the placebo patients completed the study. For study two, 79 percent of the fluoxetine patients and 78 percent of the placebo patients completed.

The primary protocol-specified outcome variable was the number of patients demonstrating at least a 50% decrease from baseline in HAMD total score. Only patients who received at least 4 weeks of treatment were to be included. The results are shown in the table below.

Protocol HCFF original sample

Study	Treatment	N randomized	N completing ≥ 4 wks	N responding	P value
1	Flx.	165	139	61	0.011
	Pbo.	164	146	43	
2	Flx.	170	146	64	0.079
	Pbo.	172	145	49	

With respect to remission, which was defined as a final HAMD-17 score of no more than 8 after at least four weeks of treatment, the results were statistically significant for both studies in favor of fluoxetine. These results are noted in the current Prozac labeling (see above). This remission variable appears to have been a post-hoc analysis, however, as I could not find a reference to it in the protocol. (Lilly reports that the current labeling is incorrect where it states that remission was defined as a HAMD of no more than 7; the present supplement corrects that error as seen above.)

With respect to mean change from baseline to endpoint in total HAMD score, neither study demonstrated superiority of fluoxetine over placebo at a statistically significant level, although there was a trend favoring the active treatment.

With respect to safety, the two studies were pooled. Adverse events occurring at a statistically significantly higher incidence with fluoxetine compared to placebo were insomnia, nausea, diarrhea, anxiety, nervousness, dyspepsia, anorexia, tremor, flatulence, sweating, abnormal vision, and impotence. (This pattern of adverse events is similar to that seen in fluoxetine clinical trials with younger subjects.) One placebo patient died from cancer, one placebo patient committed suicide 5 weeks post study and one fluoxetine patient died of congestive heart failure 4 months post study. Altogether there were 13 serious adverse events among fluoxetine patients, 11 among placebo patients, and 5 during the screening (pre-randomization) period. Note that two fluoxetine patients but no placebo patients developed atrial fibrillation; however, it is difficult from this to conclude that fluoxetine was the cause. Of the patients randomized, 11.6% of the fluoxetine group discontinued for adverse events compared to 8.6% of the placebo group.

With respect to plasma drug concentrations, these were obtained at visit 5 and visit 8 (weeks 3 and 6 of double blind fluoxetine treatment). The samples were not necessarily obtained prior to the day's dose of fluoxetine. The mean plasma concentrations and standard deviations are shown here:

Visit 5 (n=283)
Fluoxetine 237±132 mmol/l
Norfluoxetine 308+127 mmol/l

Visit 8 (n=260)
Fluoxetine 289±173 mmol/l
Norfluoxetine 405±174 mmol/l

Note that the units are mmol/l and not ng/ml. In fact, the original study report incorrectly shows the units as ng/ml (per Dr. Steve Romano of Lilly, telephone conversation 4/29/99). As stated in the current labeling, the combined fluoxetine and norfluoxetine plasma concentrations averaged 209 ± 86 ng/ml.

Reanalysis of subgroup of patients 65 years old and older

Of the 671 patients randomized in these two studies, 413 were aged 65 years or older. The numbers of patients in this age group are shown below for each study.

Study 1
Fluoxetine: 108 randomized, 82 completed
Placebo: 100 randomized, 82 completed

Study 2
Fluoxetine: 99 randomized, 76 completed
Placebo: 106 randomized, 81 completed

The number of patients demonstrating at least a 50% decrease from baseline in HAMD total score from among patients who received at least 4 weeks of treatment is shown in the next table.

Subgroup: Patients 65 years or older

Study	Treatment	N randomized	N completing ≥ 4 wks	N responding	P value
1	Flx.	108	91	40	0.131
	Pbo.	100	88	29	
2	Flx.	99	82	34	0.104
	Pbo.	106	88	26	

If the studies are pooled, however, the fluoxetine vs. placebo difference is statistically significant. This is true for the remission variable also.

With respect to safety: There do not appear to be any meaningful discrepancies in the analysis of adverse events, vital signs or clinical laboratory results when the older subgroup is compared to the entire sample. Of the patients in this subgroup, 13.0% of the fluoxetine treatment group discontinued for adverse events compared to 9.2% of the placebo group.

Pharmacokinetics

Below are the results from the reanalysis of the plasma concentration data excluding subjects aged 60-64.

Older Subgroup (aged 65 and over)
Visit 5 (n=173)
Fluoxetine 77+42 ng/ml
Norfluoxetine 93 +39 ng/ml

Visit 8 (n=158)
Fluoxetine 92+55 ng/ml
Norfluoxetine 123+51 ng/ml

Thus, the older subgroup had a combined mean fluoxetine and norfluoxetine plasma concentration of 216 ng/ml at visit 8; this is fairly close to the value of 209 ng/ml from the original, complete sample.

Additional Safety Analyses

The sponsor reviewed, in a qualitative way, the adverse events from three other controlled trials with elderly subjects; these were active controlled trials and the data were not as informative as that from study HCFF. The sponsor also analyzed their spontaneous reports database with respect to age of the patients (for the period 1984-1997). According to IMS America data, the ratio of Prozac users under age 65 compared to the number of Prozac users aged 65 years and older is — Applying this correction to U.S. spontaneous reports, the most prominent spontaneously reported adverse events in the elderly are SIADH (corrected reporting rati — versus younger patients), hyponatremia (ratio — and EPS (ratio —).

With respect to EPS, the sponsor makes several observations. First, when all U.S. placebo controlled Prozac trials are pooled (n=4397 fluoxetine and n=2918 placebo), there is a higher incidence of EPS among fluoxetine patients (1.0%) versus placebo patients (0.2%, $p<0.001$). However, most of the fluoxetine patients reporting EPS in these trials were $\leq$ 60 years old. Secondly, based on incidence in a health claims database (LifeLink), the baseline incidence of EPS appears to increase with age.

Similarly, the LifeLink data indicates a higher incidence of hyposmolality among patients aged 65 years and older, regardless of drug exposure.

The sponsor's literature search did not disclose any new information that would materially affect conclusions about fluoxetine use in the elderly.

Conclusions

The sponsor's reanalysis of study HCFF supports their proposed labeling changes. The draft labeling appears to comply with the final rule on geriatric labeling [21 CFR part 201.57(f)(10)].

It also appears that Lilly has appropriately chosen to highlight SIADH as an adverse drug reaction which may be more prominent among the elderly.

This supplement has been discussed with Dr. Greg Dubitsky, who is coordinating the geriatric labeling revisions for the psychiatric drugs.

Recommendations

The meets the requirements for geriatric labeling under the final rule, in my judgement. Parenthetically, I would note that the agency might have waived the requirement for a subgroup analysis in patients aged 65 and older had the sponsor asked, considering that the Prozac labeling already contained results from controlled trials is patients aged 60 and above. In any event, this supplement may be approved, but I recommend the following modification to the sponsor's proposed Geriatric Use section.

It would be more appropriate for the sponsor to include the standard language from the geriatric final rule in this section, which I propose should read as follows:

Geriatric use: U.S. fluoxetine clinical trials (10,782 patients) included 687 patients $\geq$ 65 years of age and 93 patients $\geq$ 75 years of age. The safety and efficacy in geriatric patients have been established (see Clinical Trials under Clinical Pharmacology). For pharmacokinetic information

in geriatric patients see Age under Clinical Pharmacology. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Fluoxetine has been associated with cases of clinically significant hyponatremia in elderly patients (see Hyponatremia under Precautions).

/S/

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

5-4/-99

/S/

NDA 18-936/S-052; 20-761-S-024
Div file
HFD-120 Laughren/Mosholder/Dubitsky/David
HFD-860 RYuan

REVIEW AND EVALUATION OF CLINICAL DATA

IND/NDA:	N18-936
SPONSOR:	Lilly
DRUG:	Fluoxetine
DRUG CATEGORY:	Selective serotonin reuptake inhibitor
MATERIAL SUBMITTED:	Geriatric Supplement Final Printed Labeling
CORRESPONDENCE DATE:	9/16/99
DATE RECEIVED:	9/17/99

SEP 23 1999

Please refer to the approvable letter for the Prozac geriatric labeling supplement, sent 8/11/99. Lilly suggested one addition to our proposed labeling: adding the phrase, "As with other SSRIs..." to the description of hyponatremia. Since other SSRIs are also associated with hyponatremia, we informed Lilly by telephone that this change was acceptable.

This submission is the final printed labeling, which incorporates the geriatric labeling specified in the approvable letter with that one modification. I recommend approval.

/S/ 9/22/99

Andrew Mosholder, MD
Medical Officer, HFD-120

9-23-99

NDA 18-936
NDA 20-101
HFD 120/TLaughren/AMosholder/PDavid

/S/

OCT - 5 1999

CSO LABELING REVIEW

Date of Review: October 5, 1999

NDA NUMBER: 18-936 (Capsules); 20-101 (liquid); 20-974 (Tablets)

Sponsor: Eli Lilly

Product Name: Trade Name: Prozac; Generic Name: fluoxetine HCl; Dosage Form: capsules/liquid/tablet

Product Indication: Antidepressant/OCD/Bulimia Nervosa

Submission Dates:

Supplement #	Submission Date	Action	Agency Letter Date
18-936/S-052 & 20-101/S-024	5-11-98	AE	8-11-99
18-936/S-052 & 20-101/S-024	9-16-99	Pending	
18-936/S-059 & 20-101/S-026	5-25-99	AP	6-16-99
18-936/S-054	2-17-99	AP	6-15-99

Materials Reviewed:

1. Last reviewed labeling for Prozac, label code PV 3310 DPP, was for the tablet formulation. An acknowledge/retain letter was issued on 5-5-99.

2. Agency letter dated 6-16-99 approving supplements 18-936/S-059 & 20-101/S-026, and Agency letter dated 6-15-99 approving supplement 18-936/S-054. These changes were submitted under 314.70(b) and therefore, the Agency requested FPL. This FPL incorporating all revisions was submitted on 7-21-99.

3. Response to Agency AE letter dated 8-11-99 for 18-936/S-052 & 20-101/S-24 in a submission dated 9-16-99. This FPL also contained the approved revisions submitted in supplements 18-936/S-054/S-059 & 20-101/S-026.

4. Medical officer's review of 9-16-99 submission to 18-936/S-052 and 20-101/S-024.

18-936/S-052 and 20-101/S-024 (Dated 8-11-99)
Label Code: PV 3312DPP
Reviewed by Medical Officer: Yes, acceptable
Changes in Effect: No

This supplement provides for the revision of the Precautions-Geriatric Use section to state the following:

Geriatric Use: U.S. fluoxetine clinical trials (10,782 patients) included 687

patients ≥ 65 years of age and 93 patients ≥ 75 years of age. The efficacy in geriatric patients has been established (see Clinical Trials under Clinical Pharmacology). For pharmacokinetic information in geriatric patients see Age under Clinical Pharmacology. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other SSRIs, fluoxetine has been associated with cases of clinically significant hyponatremia in elderly patients (see Hyponatremia under Precautions).

Conclusions/Recommendations

1. The FPL submitted on 9-16-99 (Label Code: PV 3312DPP) incorporates only those revisions listed above as well as the revisions approved in 18-936/S-059 & 20-101/S-026. Please see highlighted mark-up of this labeling compared to the last reviewed labeling for Prozac.

2. I recommend that an approval letter issue for 18-936/S-052 & 20-101/S-024.

/S/

Paul A. David, R.Ph.
Project Manager

/S/

John Purvis
Project Management Supervisor

NDA 18-936
NDA 20-101
NDA 20-974
HFD-120/Div File
09/30//99

ATTACHMENT A
DRAFT LABELING

20 page(s) of revised draft labeling has been redacted from this portion of the review.